

TRADE SECRET

Study Title

**H-28548: COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS**

Laboratory Project ID: DuPont-18405-1238

Volume 12 of 13

NUMBER OF PAGES IN VOLUME: 351

- TEST GUIDELINES:**
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
 - OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
 - JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
 - EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR: Lisa Craig, B.S.

STUDY COMPLETED ON: March 28, 2013

APPLICANT/SPONSOR: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

PERFORMING LABORATORY: MPI Research, Inc.
54943 North Main Street
Mattawan, Michigan 49071-8353
U.S.A.

WORK REQUEST NUMBER: 18405

SERVICE CODE NUMBER: 1238

MPI RESEARCH STUDY NUMBER: 125-141

Unpublished Work
Copyright ©2013 E.I. du Pont de Nemours and Company

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1519	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1520	S	Macroscopic mammary gland	- swollen/thickened, tan, generalized, mild corresponds to antemortem observation (swelling)
1520	S	Microscopic adrenal glands kidneys	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1520	S	Microscopic liver	- focus of cellular alteration, basophilic, mild - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal
		lung	- hyperplasia, lobular, mild
		mammary gland	- corresponds to macroscopic observation (mammary gland - swollen/thickened)
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1521	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Macroscopic lymph node, inguinal skin, subcutis	- within normal limits draining node for mass b, right. - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 7.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 11.0 x 6.0 x 4.0 cm.
1521	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hematopoiesis, extramedullary, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - necrosis, focal, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1521	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1521	E	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - metaplasia, squamous, minimal - within normal limits - mammary tumor
1522	E	Macroscopic animal/whole body lymph node, inguinal pituitary gland skin, subcutis	- body fat depleted, moderate corresponds to antemortem observation (thin) - within normal limits draining node for mass a, left. - enlarged, red, severe - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter.

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic kidneys	- dilatation, tubular, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- within normal limits
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1522	E	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass a, right, and mass c, right. - within normal limits draining node for mass b, right. - enlarged, red, mild - mass, black, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 4.5 x 4.0 x 2.0 cm. - mass, black, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 4.5 x 4.5 x 3.0 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (nodule) approximately 0.8 x 0.5 x 0.5 cm.
1523	E	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, moderate - hypertrophy, focal cortical, unilateral, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c) - galactoceles, moderate corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1523	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1523	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- hyperplasia, epithelial cell, mild
		tongue	- adenoma, c-cell, benign, bilateral, primary, incidental, not cause of death
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- dilatation, gland/lumen, minimal
		Cause of Death	- within normal limits
1524	E	Macroscopic lymph node, axillary	- mammary tumor
		lymph node, inguinal	- within normal limits draining node for mass a, left.
			- within normal limits draining node for mass b, right.
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Macroscopic mammary gland pituitary gland skin, subcutis	- swollen/thickened, tan, generalized, moderate corresponds to antemortem observation (hair sparse swelling) - enlarged, moderate - mass, tan, mass b, right inguinal area, present approximately 1.0 cm in diameter. - mass, ulcerated, left axillary area, mass a, present corresponds to antemortem observation (mass 1) approximately 2.0 x 1.0 x 1.0, tan. - enlarged, horn, moderate
1524	E	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, inguinal	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - atrophy, acinar, minimal - not examined - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1524	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
		vagina Cause of Death	- within normal limits - mammary tumor
1525	E	Macroscopic lymph node, axillary pituitary gland skin, subcutis	- within normal limits left, draining node for mass a. - enlarged, red, severe - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (nodule swelling) approximately 1.0 x 1.0 x 0.5 cm.

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, moderate - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1525	E	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1525	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - pituitary tumor
1526	E	Macroscopic lymph node, inguinal pituitary gland	- not identified, bilateral, no grade draining node for mass a, left and mass b, right. - enlarged, moderate

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Macroscopic skin, subcutis	- mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 cm in diameter - mass, tan, mass b, right inguinal area, present approximately 2.0 cm in diameter.
1526	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - exudate, nasal passage, moderate - inflammation, mild - exudate, nasal passage, moderate - inflammation, minimal - exudate, nasal passage, minimal - exudate, nasal passage, minimal - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1526	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1526	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- hyperplasia, epithelial cell, minimal
		tongue	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1527	E	Macroscopic ears	- nodule, tan, left, present corresponds to antemortem observation (nodule) approximately 0.4 cm in diameter.
		lymph node, axillary	- within normal limits draining node for mass b, right.

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, red, moderate - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 2.5 cm in diameter. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (mass 2) approximately 8.5 x 9.0 x 3.5 cm.
1527	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in RatsIndividual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic liver	- focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - vacuolation, periportal, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - hyperplasia, acinar cell, focal, moderate - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (ears - nodule) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1527	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1528	S	Macroscopic lymph node, inguinal	- not identified, right, no grade draining node for mass a.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1528	S	Macroscopic skin, subcutis	- mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 8.0 x 7.0 x 4.5 cm.
1528	S	spleen uterus with cervix Microscopic adrenal glands kidneys liver lung mammary gland pancreas	- enlarged, mild - enlarged, cervix, mild - hyperplasia, focal medullary, bilateral, mild - dilatation, tubular, bilateral, mild - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, acinar cell, focal, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1528	S	Microscopic spleen stomach, nonglandular tongue uterus with cervix	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - dilatation, gland/lumen, moderate corresponds to macroscopic observation (uterus with cervix - enlarged) - hyperplasia, cervical fibromuscular, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - hyperplasia, squamous cell, minimal
1529	E	Macroscopic pituitary gland	- enlarged, moderate
1529	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in RatsIndividual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - focus of cellular alteration, clear, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1529	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1529	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1530	E	Macroscopic pituitary gland	- enlarged, red, moderate
1530	E	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, focal, unilateral, minimal - within normal limits - within normal limits - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, mild - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1530	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1530	E	Microscopic thymus	- depletion, lymphoid, generalized, moderate
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- hyperplasia, c-cell, focal, unilateral, mild
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1531	E	Macroscopic mammary gland	- swollen/thickened, tan, left axillary area, mild corresponds to antemortem observation (swelling)
		pituitary gland	- enlarged, red, severe
		stomach, nonglandular	- irregular surface, tan, mild
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
		kidneys	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - vacuolation, periportal, minimal - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1531	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hyperplasia, epithelial, nonglandular, moderate corresponds to macroscopic observation (stomach, nonglandular - irregular surface) - inflammation, mild - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1532	S	Macroscopic lymph node, axillary	- within normal limits draining node for mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1532	S	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - not identified, left, no grade draining node for mass c and mass d. - within normal limits draining node for mass a, right. - enlarged, red, mild - mass, tan, mass a, right lateral neck, present corresponds to antemortem observation (mass 1) approximately 6.0 x 5.0 x 2.5 cm. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (swelling) approximately 2.5 cm in diameter. - mass, tan, mass c, left inguinal area, present approximately 3.0 x 3.0 x 1.0 cm. - mass, tan, mass d, left anogenital region, present approximately 2.5 cm in diameter.
1532	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1532	S	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
		liver	- hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal
		lung	- within normal limits
		lymph node, axillary	- within normal limits
		lymph node, mandibular	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1532	S	Microscopic uterus with cervix	- within normal limits
1533	E	Macroscopic lymph node, axillary skin, subcutis	- within normal limits draining node for mass a, left. - mass, ulcerated, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 7.0 x 7.0 x 3.0 cm, tan.
1533	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, minimal
		nose, level a	- degeneration, axonal/myelin, minimal
			- exudate, nasal passage, mild
			- foreign material, minimal plant.
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, minimal
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- within normal limits
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141

Dupont-18405-1238

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1533	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1533	E	Microscopic vagina Cause of Death	- within normal limits - mammary tumor
1534	D	Macroscopic pituitary gland	- enlarged, moderate
1534	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), severe - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - exudate, luminal, minimal - inflammation, minimal - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - vacuolation, periportal, mild - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - mucus increased, mild - mucus increased, mild - cyst, unilateral, mild - hyperplasia, sex-cord/stromal, bilateral, mild - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1534	D	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - inflammation, acute, minimal - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1535	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass a, left.
		skin, subcutis	- mass, ulcerated, mass a, left lateral neck, present corresponds to antemortem observation (mass 1) approximately 8.0 x 7.0 x 5.0 cm, tan.
1535	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - necrosis, hepatocytes, centrilobular, moderate - histiocytosis, alveolar, minimal - hyperplasia, lymphocyte/plasmacyte, medulla, mild - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1535	E	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1535	E	Microscopic Cause of Death	- mammary tumor
1536	E	Macroscopic pituitary gland skin	- enlarged, moderate - hair sparse, generalized, mild corresponds to antemortem observation (hair sparse) most affected areas dorsal cervical, forelimbs bilateral and shoulders bilateral.
1536	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hydronephrosis, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, mild - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1536	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in RatsIndividual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1536	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1537	E	Macroscopic pituitary gland	- enlarged, severe
1537	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - nephropathy, chronic progressive, bilateral, minimal - pyelitis, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - vacuolation, periportal, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1537	E	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1537	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1538	S	Macroscopic adrenal glands mammary gland ovaries pancreas spleen	- enlarged, left, moderate - swollen/thickened, mild right and left inguinal and axillary region mostly affected. - cyst, clear, left, mild - cyst, red, multiple, mild - focus/foci, white, mild
1538	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - atrophy, cortical, unilateral, moderate
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1538	S	Microscopic kidneys	<ul style="list-style-type: none"> - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - polyarteritis, bilateral, moderate renal artery.
		liver	<ul style="list-style-type: none"> - pyelitis, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal
		lung	<ul style="list-style-type: none"> - hyperplasia, bile duct, minimal
		lymph node, mesenteric	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal
		mammary gland	<ul style="list-style-type: none"> - dilatation, sinus, mild - corresponds to macroscopic observation (pancreas - cyst) - fibroadenoma, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (mammary gland - swollen/thickened) - hyperplasia, lobular, moderate - corresponds to macroscopic observation (mammary gland - swollen/thickened)
		ovaries	<ul style="list-style-type: none"> - cyst, unilateral, mild - corresponds to macroscopic observation (ovaries - cyst) - hyperplasia, sex-cord/stromal, unilateral, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1538	S	Microscopic pancreas	- atrophy, acinar, minimal - polyarteritis, moderate corresponds to macroscopic observation (pancreas - cyst)
		spleen	- fibrosis, capsular, mild corresponds to macroscopic observation (spleen - focus/foci, white)
		stomach, nonglandular tongue	- hematopoiesis, extramedullary, increased, minimal - within normal limits
		uterus with cervix	- within normal limits - dilatation, gland/lumen, minimal
1539	E	Macroscopic lung with bronchi	- discoloration, pink, azygous lobe, moderate
		lymph node, axillary	- within normal limits draining node for mass a, right and mass c, left.
		lymph node, mandibular	- within normal limits draining node for mass b, left.
		pituitary gland	- enlarged, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Macroscopic skin skin, subcutis	<ul style="list-style-type: none"> - abrasion/scab, right lateral head, moderate corresponds to antemortem observation (abrasion(s) swelling) - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 6.0 x 4.0 x 3.0 cm. - mass, tan, mass b, left lateral neck, present approximately 1.5 x 1.5 x 0.5 cm. - mass, tan, mass c, left axillary area, present corresponds to antemortem observation (swelling) approximately 1.0 cm in diameter.
1539	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - vacuolation, periportal, mild - histiocytosis, alveolar, minimal
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, squamous cell, malignant, primary, mortality-independent corresponds to macroscopic observation (skin - abrasion/scab) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1539	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lung with bronchi - discoloration, pink - skin tumor
1540	E	Macroscopic lymph node, axillary	- within normal limits right is draining node for mass c.

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits right is draining node for mass a, left is draining node for mass b. - enlarged, red, severe - mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 x 3.0 x 3.0 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (mass 3) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.5 x 2.0 x 1.5 cm and tan in color.
1540	E	Microscopic adrenal glands aorta bone marrow, femur	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, axillary	<ul style="list-style-type: none"> - not examined - not found at the time of trimming
		lymph node, inguinal	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c)
		nerve, sciatic	<ul style="list-style-type: none"> - degeneration, axonal/myelin, minimal
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1540	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - mammary tumor
1541	S	Macroscopic adrenal glands	- enlarged, red, right, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Macroscopic lymph node, mandibular mammary gland pituitary gland skin, subcutis	<ul style="list-style-type: none"> - within normal limits draining node for mass a, right. draining node for mass b, left. - swollen/thickened, tan, generalized, moderate - enlarged, red, mild - mass, tan, mass a, right lateral neck, present corresponds to antemortem observation (swelling) approximately 2.3 cm in diameter. - mass, tan, mass b, left lateral neck, present approximately 2.0 cm in diameter.
1541	S	Microscopic adrenal glands kidneys	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - atrophy, cortical, unilateral, moderate - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Microscopic liver	<ul style="list-style-type: none"> - focus of cellular alteration, basophilic, mild - focus of cellular alteration, clear, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (mammary gland - swollen/thickened) - fibroadenoma, benign, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - corresponds to macroscopic observation (mammary gland - swollen/thickened)
		pancreas	<ul style="list-style-type: none"> - atrophy, acinar, minimal - hyperplasia, acinar cell, focal, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1541	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1542	D	Macroscopic mammary gland pituitary gland skin	- swollen/thickened, generalized, mild - enlarged, red, severe - abrasion/scab, dorsal thoracic region, mild - hair sparse, neck, shoulder, right, mild corresponds to antemortem observation (hair sparse)
1542	D	Microscopic adrenal glands aorta	- within normal limits - within normal limits

S - Scheduled necropsy
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1542	D	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1542	D	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - skin - abrasion/scab - pituitary tumor
1543	S	Macroscopic adrenal glands pituitary gland	- enlarged, left, mild - cyst, clear, mild
1543	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1543	S	Microscopic kidneys liver lung pancreas pituitary gland stomach, nonglandular tongue uterus with cervix	- mineralization, pelvic, bilateral, minimal - hyperplasia, bile duct, minimal - within normal limits - atrophy, acinar, minimal - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - cyst) - within normal limits - within normal limits - within normal limits
1544	E	Macroscopic pituitary gland skin	- enlarged, severe - nodule, tan, nose/muzzle, present corresponds to antemortem observation (nodule) approximately 0.2 cm in diameter.
1544	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, unilateral, minimal - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- hyperplasia, epidermal, moderate corresponds to macroscopic observation (skin - nodule)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1544	E	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1545	D	Macroscopic eyes eyes, optic nerves eyes, retina	- absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized) - absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized) - absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Macroscopic lacrimal glands, exorbital	- absent/cannibalized, right, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, mandibular	- absent/cannibalized, bilateral, no grade
		salivary gland, parotid	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		salivary gland, sublingual	- absent/cannibalized, bilateral, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
1545	D	Microscopic adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits one of pair present - within normal limits one of pair present - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- bacterial colonies, minimal areas with lysis of red blood cells indicative of dosing injury. - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined cannibalized
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1545	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- not examined cannibalized - not examined cannibalized - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1545	D	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1546	S	Macroscopic pituitary gland uterus with cervix	- enlarged, red, mild - enlarged, horn, mild
1546	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal cortical, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1546	S	Microscopic kidneys	- hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		liver	- fibrosis, minimal - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - necrosis, focal, minimal
		lung	- within normal limits
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1547	S	Macroscopic adrenal glands pituitary gland	- enlarged, left, mild - enlarged, severe
1547	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
		kidneys	- cyst, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal
		liver	- nephropathy, chronic progressive, unilateral, minimal - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal
		lung	- hyperplasia, bile duct, minimal - within normal limits
		pancreas	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1547	S	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1548	E	Macroscopic lymph node, inguinal	- not identified, right, no grade draining node for mass a and mass c. draining node for mass b, left.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 9.0 x 5.0 x 3.0 cm. - mass, tan, mass b, left anogenital region, present approximately 3.0 cm in diameter. - mass, tan, mass c, right inguinal area, present approximately 2.0 x 1.5 x 1.0 cm.
1548	E	spleen uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	<ul style="list-style-type: none"> - enlarged, minimal - enlarged, horn, mild - angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, bilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - vacuolation, periportal, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged)
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, moderate hyperplasia, epithelial cell, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1548	E	Microscopic thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, c-cell, focal, unilateral, mild
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged)
		vagina	- granular cell tumor, benign, primary, incidental, not cause of death
		Cause of Death	- mammary tumor
1549	S	Macroscopic adrenal glands lymph node, inguinal	- focus/foci, red, left, mild - not identified, bilateral, no grade draining node for mass a, left and mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1549	S	Macroscopic pituitary gland skin, subcutis	<ul style="list-style-type: none"> - enlarged, mild - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 5.0 x 4.0 x 3.0 cm. - mass, tan, mass b, right anogenital region, present approximately 1.5 cm in diameter.
1549	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - focus/foci, red) - hyperplasia, focal medullary, unilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - focus of cellular alteration, basophilic, mild - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1549	S	Microscopic mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		pancreas	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1550	D	Macroscopic lymph node, axillary	- within normal limits draining node for mass b, left.
		lymph node, inguinal	- not identified, left, no grade draining node for mass a.
		pituitary gland	- enlarged, red, severe

S - Scheduled necropsy
D - Died on Study

MPI Research Study Number 125-141

Dupont-18405-1238

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Macroscopic skin, subcutis	- mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 2.0 cm. - mass, tan, mass b, left axillary area, present corresponds to antemortem observation (nodule) approximately 1.0 cm in diameter.
1550	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic mammary gland	- adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- cyst, unilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1550	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1550	D	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - metaplasia, squamous, minimal - within normal limits - pituitary tumor
1551	E	Macroscopic lung with bronchi lymph node, iliac ovaries	- focus/foci, red, multiple lobes, mild - within normal limits draining node for mass a, left. - mass, red, mass a, left, present approximately 2.0 cm in diameter.
1551	E	stomach, nonglandular Microscopic adrenal glands aorta bone marrow, femur	- focus/foci, tan, mild - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - hyaline, droplets, increased, bilateral, mild - lymphoma, malignant, bilateral, multicentric, fatal, positive cause of death - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mediastinal lymph node, mesenteric mammary gland multicentric neoplasm nerve, sciatic nose, level a	- within normal limits - within normal limits - inflammation, minimal - focus of cellular alteration, basophilic, minimal - lymphoma, malignant, multicentric, fatal, positive cause of death - congestion, chronic passive, severe - lymphoma, malignant, multicentric, fatal, positive cause of death corresponds to macroscopic observation (lung with bronchi - focus/foci, red) - within normal limits - lymphoma, malignant, multicentric, fatal, positive cause of death - lymphoma, malignant, multicentric, fatal, positive cause of death slide 14. - erythrocytosis/erythrophagocytosis, sinus, mild - lymphoma, malignant, multicentric, fatal, positive cause of death - hyperplasia, lobular, mild - lymphoma, malignant, multicentric, fatal, positive cause of death - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - sex-cord/stromal tumor, malignant, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (ovaries - mass a) slide 15 and 26-1. - within normal limits - atrophy, acinar, minimal - fibrosis, minimal - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1551	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erosion/ulcer, severe corresponds to macroscopic observation (stomach, nonglandular - focus/foci, tan) - erosion/ulcer, limiting ridge, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1551	E	Microscopic vagina Cause of Death	- within normal limits - lymphoid tumor
1552	E	Macroscopic pituitary gland	- enlarged, severe
1552	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1552	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1552	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1552	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - pituitary tumor
1553	S	Macroscopic adrenal glands	- enlarged, left, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1553	S	Macroscopic lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass b, right. draining node for mass c, left. - within normal limits draining node for mass a, right. - enlarged, red, moderate - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter. - mass, tan, mass b, right axillary area, present approximately 1.2 cm in diameter. - mass, tan, mass c, left axillary area, present approximately 1.8 cm in diameter.
1553	S	Microscopic adrenal glands kidneys	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1553	S	Microscopic liver	- infiltration, mononuclear cell, minimal - vacuolation, periportal, minimal
		lung	- within normal limits
		lymph node, axillary	- within normal limits
		lymph node, inguinal	- within normal limits
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c)
		pancreas	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b)
		pituitary gland	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, red, severe - mass, tan, mass a, right anogenital region, present approximately 3.5 cm in diameter.
1554	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1554	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1554	E	Microscopic vagina Cause of Death	- within normal limits - pituitary tumor
1555	D	Macroscopic pituitary gland skin thymus	- enlarged, red, moderate - hair sparse, dorsal cervical region, dorsal head, mild corresponds to antemortem observation (hair sparse) - small, moderate
1555	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1555	D	Microscopic skin	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse)
			- cyst, keratin, minimal
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small)
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1555	D	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1556	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland	- not identified, right, no grade draining node for mass c and mass d. draining node for mass a, left. - within normal limits draining node for mass b, right. - enlarged, mild

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, right anogenital region, mass c, present approximately 1.2 cm in diameter. - mass, tan, right inguinal area, mass d, present approximately 1.4 cm in diameter. - mass, tan, right lateral neck, mass b, present corresponds to antemortem observation (nodule) approximately 1.2 cm in diameter. - mass, ulcerated, left anogenital region, mass a, present corresponds to antemortem observation (mass 1 skin discolored) approximately 3.0 cm in diameter, tan.
1556	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic lymph node, mesenteric mammary gland	- within normal limits - adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass c; skin, subcutis - mass d) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- atrophy, acinar, mild
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1556	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1556	E	Microscopic thymus	- depletion, lymphoid, generalized, severe
			- hyperplasia, epithelial cell, minimal
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- metaplasia, squamous, minimal
		vagina	- within normal limits
		Cause of Death	- mammary tumor
1557	E	Macroscopic pituitary gland	- enlarged, red, severe
		stomach, nonglandular	- irregular surface, mild
1557	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, mild - mineralization, pelvic, bilateral, minimal - pyelitis, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - infiltration, mononuclear cell, minimal - necrosis, focal, minimal - vacuolation, periportal, mild - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1557	E	Microscopic stomach, nonglandular	- hyperplasia, epithelial, nonglandular, moderate corresponds to macroscopic observation (stomach, nonglandular - irregular surface) - inflammation, mild corresponds to macroscopic observation (stomach, nonglandular - irregular surface)
		thymus	- depletion, lymphoid, generalized, moderate
		thyroid gland	- carcinoma, c-cell, malignant, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1558	E	Macroscopic adrenal glands	- enlarged, left, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Macroscopic cavity, thoracic kidneys liver lymph node, axillary lymph node, inguinal pituitary gland skin, subcutis spleen	- fluid, clear, minimal approximately 1.0 ml. - discoloration, tan, bilateral, minimal - discoloration, tan, multiple lobes, minimal - within normal limits draining node for mass a, left. - within normal limits draining node for mass b, left. - enlarged, red, moderate - mass, scabbed, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 20.0 cm in diameter, tan. - mass, tan, mass b, left anogenital region, present approximately 2.0 x 1.0 x 1.0 cm. - enlarged, mild
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic adrenal glands	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (adrenal glands - enlarged) - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - hematopoiesis, extramedullary, bilateral, minimal - hyperplasia, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	<ul style="list-style-type: none"> - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - hyaline, droplets, increased, bilateral, mild - corresponds to macroscopic observation (kidneys - discoloration, tan) - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - infiltration, mononuclear cell, minimal - necrosis, hepatocytes, centrilobular, mild - corresponds to macroscopic observation (liver - discoloration, tan) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1558	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		skin, subcutis	- fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild corresponds to macroscopic observation (spleen - enlarged)
		stomach, glandular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u>			
1558	E	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - fibrosarcoma/fibroma
1559	S	Macroscopic lymph node, inguinal	- not identified, bilateral, no grade draining node for mass a, right. draining node for mass b, left.
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1559	S	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.5 x 5.5 x 3.0 cm. - mass, tan, mass b, left inguinal area, present approximately 1.0 cm in diameter.
1559	S	Microscopic adrenal glands kidneys liver lung	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, unilateral, moderate - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1559	S	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		pancreas	- within normal limits
		stomach, nonglandular	- within normal limits
		tongue	- within normal limits
		uterus with cervix	- within normal limits
1560	E	Macroscopic adrenal glands	- enlarged, tan, right, mild
		lymph node, mandibular	- not identified, bilateral, no grade draining node for mass a.
		pituitary gland	- enlarged, tan, mild
		skin, subcutis	- mass, ulcerated, mass a, ventral neck, present corresponds to antemortem observation (mass 1) approximately 5.0 x 4.5 x 3.0 cm, tan.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- hyperplasia, focal cortical, unilateral, minimal
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- hyperplasia, granulocytic, mild
		bone, femur	- hyperplasia, granulocytic, mild
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hematopoiesis, extramedullary, minimal - within normal limits - not examined - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>50 mg/kg/day</u> 1560	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Macroscopic skin	- hair sparse, dorsal cervical region, dorsal head, moderate corresponds to antemortem observation (hair sparse)
1566	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits

D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - within normal limits lysis of red blood cells within capillaries. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - polyarteritis, mild - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1566	D	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1567	D	Macroscopic kidneys	- irregular surface, bilateral, mild
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Macroscopic lung with bronchi pituitary gland skin	- discoloration, red, multiple lobes, moderate - enlarged, minimal - hair sparse, head, right lateral thorax, moderate corresponds to antemortem observation (hair sparse)
1567	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- cardiomyopathy, minimal - within normal limits - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1567	D	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits - lung with bronchi - discoloration, red - pituitary gland - enlarged - dosing injury
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Macroscopic adrenal glands brain kidneys liver lung with bronchi lymph node, axillary lymph node, iliac lymph node, inguinal lymph node, mesenteric pancreas pituitary gland	- enlarged, left, mild - discoloration, tan, moderate - discoloration, tan, pelvis, bilateral, mild - focus/foci, tan, median lobe, right lateral lobe, mild - nodule, tan, left lateral lobe, present approximately 0.4 cm in diameter. - discoloration, pink, multiple lobes, mild - within normal limits draining node for mass b, right. - within normal limits draining node for mass d. - not identified, left, no grade draining node for mass a. - within normal limits draining node for mass c. - mass, tan, mass c, present approximately 0.6 cm in diameter. - enlarged, red, severe

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 7.5 x 6.0 x 3.0 cm, tan.
1573	E	uterus with cervix	<ul style="list-style-type: none"> - mass, tan, mass d, present approximately 4.0 cm in diameter.
		Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	<ul style="list-style-type: none"> - within normal limits
		bone marrow, femur	<ul style="list-style-type: none"> - hyperplasia, granulocytic, mild
		bone marrow, sternum	<ul style="list-style-type: none"> - within normal limits
		bone, femur	<ul style="list-style-type: none"> - within normal limits
		bone, sternum	<ul style="list-style-type: none"> - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild corresponds to macroscopic observation (kidneys - discoloration, tan) - edema, papilla, bilateral, mild corresponds to macroscopic observation (kidneys - discoloration, tan) - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, iliac lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - adenoma, hepatocellular, benign, primary, incidental, not cause of death corresponds to macroscopic observation (liver - nodule) - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild - necrosis, hepatocytes, centrilobular, mild corresponds to macroscopic observation (liver - focus/foci, tan) - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	<ul style="list-style-type: none"> - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1573	E	Microscopic uterus with cervix	- carcinoma, squamous cell, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - mass d)
		vagina	- within normal limits
		non-correlated macro observation	- brain - discoloration, tan - lung with bronchi - discoloration, pink - pancreas - mass c - mammary tumor
		Cause of Death	
1574	E	Macroscopic pituitary gland	- enlarged, red, severe
1574	E	Microscopic adrenal glands	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death - angiectasis/cystic degeneration, focal cortical, unilateral, moderate

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	 - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1574	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- hyperplasia, epithelial, limiting ridge, minimal
		thymus	- depletion, lymphoid, generalized, moderate

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1574	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hyperplasia, c-cell, focal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1575	D	Macroscopic all tissues	- within normal limits
1575	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, lymphoid, medulla, mild
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1575	D	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - hyperplasia, simple transitional cell, mild - within normal limits - within normal limits - kidney inflammation/necrosis
1576	S	Macroscopic kidneys liver lymph node, inguinal skin, subcutis	- irregular surface, bilateral, mild - focus/foci, tan, multiple lobes, mild - not identified, left, no grade draining node for mass a. - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 5.0 x 9.0 x 8.0 cm.
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - focus/foci, tan) - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, moderate - corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, panlobular, mild - infiltration, mononuclear cell, minimal - necrosis, individual hepatocyte, mild - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- fibroadenoma, benign, primary, mortality-independent
		mammary gland	- corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
			- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1576	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits
1577	E	Macroscopic lung with bronchi	- discoloration, tan, multiple lobes, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Macroscopic lymph node, iliac lymph node, inguinal skin, subcutis	- within normal limits draining node for mass a, left. - not identified, right, no grade draining node for mass b. - abscess, left inguinal area, moderate corresponds to antemortem observation (nodule) - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1 swelling) approximately 5.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 cm in diameter.
1577	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - hyperplasia, focal medullary, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic kidneys	<ul style="list-style-type: none"> - cyst, unilateral, mild - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, mild - hyperplasia, bile duct, mild - hypertrophy, hepatocyte, panlobular, mild - necrosis, hepatocytes, centrilobular, mild
		lung	- histiocytosis, alveolar, minimal
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - abscess; skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1577	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1577	E	Microscopic uterus with cervix vagina non-correlated macro observation Cause of Death	- metaplasia, squamous, minimal - within normal limits - lung with bronchi - discoloration, tan - mammary tumor
1578	S	Macroscopic kidneys	- irregular surface, bilateral, mild
1578	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, mild - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - cyst, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1578	S	Microscopic uterus with cervix vagina	- hyperkeratosis, minimal - hyperplasia, squamous cell, mild - within normal limits
1579	E	Macroscopic kidneys lymph node, axillary pituitary gland skin skin, subcutis	- irregular surface, bilateral, mild - not identified, right, no grade draining node for mass a - enlarged, red, moderate - hair sparse, ventral abdomen, mild corresponds to antemortem observation (hair sparse) - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 6.0 x 5.0 x 4.0 cm, tan
1579	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1579	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, lymphoid, medulla, mild - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1579	E	Microscopic ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hyperplasia, endometrial, mild - hyperplasia, squamous cell, mild - within normal limits - mammary tumor
1580	E	Macroscopic pituitary gland	- enlarged, moderate
1580	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1580	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1580	E	Microscopic vagina Cause of Death	- within normal limits - pituitary tumor
1581	S	Macroscopic all tissues	- within normal limits
1581	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- hyperplasia, focal medullary, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1581	S	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1582	E	Macroscopic kidneys	- irregular surface, bilateral, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1582	E	Macroscopic pituitary gland	- enlarged, severe
1582	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - degeneration, cystic, focal, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	<ul style="list-style-type: none"> - infiltration, mononuclear cell, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, unilateral, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1582	E	Microscopic urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - pituitary tumor
1583 ^r	E	Macroscopic kidneys lymph node, axillary lymph node, inguinal pituitary gland	- irregular surface, bilateral, mild - enlarged, right, mild draining node for mass a. - not identified, right, no grade draining node for mass b. - enlarged, mild

E - Euthanized *in extremis*
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - abscess, left axillary area, mild - mass, red, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 2.0 cm in diameter. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 2.5 x 4.0 x 1.0 cm, tan.
1583 ^r	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	<ul style="list-style-type: none"> - hematopoiesis, extramedullary, bilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, bilateral, moderate corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic liver	- hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, axillary	- hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, axillary - enlarged)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, minimal - within normal limits
		nose, level a	- inflammation, hair follicle/epidermis, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits

E - Euthanized *in extremis*
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - abscess, mild corresponds to macroscopic observation (skin, subcutis - abscess) - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1583 ^r	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1584 ^r	D	Macroscopic kidneys	- irregular surface, tan, bilateral, mild

E - Euthanized *in extremis*
D - Died on Study
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits

D - Died on Study
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, mild - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal

D - Died on Study
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study ^r Replacement animal			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1584 ^r	D	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidney inflammation/necrosis

D - Died on Study
^r Replacement animal

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Macroscopic liver	- mass, tan, mass a, right lateral lobe, present approximately 2.5 cm in diameter. - mass, tan, mass b, median lobe, present approximately 0.7 cm in diameter. - not identified, no grade draining node for mass a and mass b.
1585	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, unilateral, mild - edema, papilla, bilateral, mild - necrosis, papillary, unilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic liver	- adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass a; liver - mass b) - degeneration, cystic, focal, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild - histiocytosis, alveolar, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- hyperplasia, sex-cord/stromal, unilateral, minimal
		oviducts	- within normal limits
		pancreas	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1585	S	Microscopic thymus	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
1586	D	Macroscopic adrenal glands	- enlarged, red, right, minimal
		foot/feet	- absent portion/cannibalized, left foreleg/limb, no grade corresponds to antemortem observation (cannibalized/partially cannibalized)
		pituitary gland	- enlarged, red, mild

S - Scheduled necropsy
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - hyperplasia, focal cortical, unilateral, minimal - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined autolysis too severe for diagnosis
		galt	- not examined
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - not examined - within normal limits - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - not examined - within normal limits - not examined - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1586	D	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - erosion/ulcer, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Macroscopic adrenal glands liver lymph node, hepatic lymph node, inguinal mammary gland skin, subcutis	- enlarged, bilateral, mild - mass, red, mass b, caudate lobe, present approximately 3.5 cm in diameter. - within normal limits draining node for mass b. - within normal limits draining node for mass a, right. - swollen/thickened, tan, generalized, mild corresponds to antemortem observation (swelling) - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (nodule) approximately 1.5 cm in diameter.
1587	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass b) - focus of cellular alteration, clear, minimal - focus of cellular alteration, eosinophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, hepatic	<ul style="list-style-type: none"> - within normal limits
		lymph node, inguinal	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - fibroadenoma, benign, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a) - mammary tumor on 18 r-1 and 26-1 are the same tumor. - hyperplasia, lobular, minimal
		nerve, sciatic	<ul style="list-style-type: none"> - degeneration, axonal/myelin, minimal
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - hyperplasia, sex-cord/stromal, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1587	S	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation	- within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild - within normal limits - adrenal glands - enlarged - mammary gland - swollen/thickened
1588	E	Macroscopic liver	- enlarged, multiple lobes, moderate

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Macroscopic lymph node, axillary skin, subcutis	- within normal limits draining node for mass a, right. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 11.0 cm in diameter, tan.
1588	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, minimal - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild corresponds to macroscopic observation (liver - enlarged) - necrosis, focal, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- histiocytosis, alveolar, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits - within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1588	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1588	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - mammary tumor
1589	E	Macroscopic adrenal glands kidneys liver ovaries pituitary gland	- enlarged, red, right, mild - cyst, clear, bilateral, moderate - focus/foci, tan, left lateral lobe, mild - cyst, clear, right, mild - enlarged, severe
1589	E	Microscopic adrenal glands aorta bone marrow, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, moderate corresponds to macroscopic observation (kidneys - cyst) - edema, papilla, bilateral, mild - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, bilateral, moderate - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	- within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - focus of cellular alteration, basophilic, moderate corresponds to macroscopic observation (liver - focus/foci, tan) - focus of cellular alteration, eosinophilic, moderate corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- cyst, unilateral, minimal corresponds to macroscopic observation (ovaries - cyst) - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1589	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - pituitary tumor
1590	E	Macroscopic adrenal glands	- enlarged, right, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Macroscopic lymph node, inguinal skin, subcutis	- not identified, right, no grade draining node for mass a. - mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter. red.
1590	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged) - pheochromocytoma, benign, unilateral, primary, incidental, not cause of death - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic liver	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1590	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1590	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1591	D	Macroscopic all tissues	- within normal limits
1591	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, mild - within normal limits - within normal limits - not examined - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - necrosis, papillary, bilateral, moderate - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, mild - within normal limits one of pair present
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1591	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue	 - within normal limits - hyperplasia, focal, pars distalis, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1591	D	Microscopic trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidney inflammation/necrosis
1592	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis stomach, glandular	- not identified, right, no grade draining node for mass b. draining node for mass a, left. - enlarged, mild - mass, tan, mass b, right inguinal area, present approximately 2.5 cm in diameter. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter, tan. - swollen/thickened, mucosa, mild

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1592	E	Macroscopic thymus	- small, moderate
1592	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- not examined
		heart	- within normal limits
		joint, tibiofemoral	- within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic kidneys	<ul style="list-style-type: none"> - cyst, unilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - macrophages, pigmented, minimal - necrosis, individual hepatocyte, minimal
		lung	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, moderate
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death - hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged) adenoma is small.
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1592	E	Microscopic stomach, glandular	- fibrosis, mild corresponds to macroscopic observation (stomach, glandular - swollen/thickened)
		stomach, nonglandular	- within normal limits
		thymus	- not examined
		thyroid gland	- within normal limits
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, minimal
		vagina	- within normal limits
		non-correlated macro observation	- thymus - small
		Cause of Death	- mammary tumor
1593	S	Macroscopic adrenal glands	- cyst, clear, right, mild - enlarged, left, mild

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Macroscopic kidneys lymph node, inguinal skin, subcutis	- irregular surface, bilateral, mild - within normal limits draining node for mass a, left. - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (swelling) approximately 4.0 x 3.5 x 1.5 cm.
1593	S	Microscopic adrenal glands aorta bone marrow, femur	- adenoma, cortical, benign, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (adrenal glands - enlarged) - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst) - atrophy, cortical, unilateral, moderate one medulla present - within normal limits - hyperplasia, granulocytic, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hydronephrosis, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - corresponds to macroscopic observation (kidneys - irregular surface)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hypertrophy, hepatocyte, centrilobular, minimal
		lung	- granuloma, minimal
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1593	S	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - dilatation, unilateral, mild - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1593	S	Microscopic vagina	- within normal limits
1594	S	Macroscopic all tissues	- within normal limits
1594	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - angiectasis, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1594	S	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, mild - within normal limits - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1594	S	Microscopic uterus with cervix	- dilatation, gland/lumen, minimal - hyperplasia, squamous cell, mild - within normal limits
		vagina	
1595	S	Macroscopic adrenal glands	- enlarged, right, moderate - within normal limits
		lymph node, mesenteric	draining node for mass a.
		stomach, nonglandular	- mass, tan, mass a, present approximately 0.8 cm in diameter.
1595	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141

Dupont-18405-1238

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, mild - within normal limits - detachment, retinal, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic liver	- angiectasis, mild - focus of cellular alteration, basophilic, mild - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
S - Scheduled necropsy			

MPI Research Study Number 125-141

Dupont-18405-1238

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1595	S	Microscopic salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue	 - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - cyst, keratin, moderate corresponds to macroscopic observation (stomach, nonglandular - mass a) - depletion, lymphoid, generalized, moderate - hyperplasia, follicular cell, unilateral, minimal - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1595	S	Microscopic trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1596	D	Macroscopic animal/whole body kidneys lacrimal glands, exorbital lung with bronchi spleen thymus	- body fat depleted, mild corresponds to antemortem observation (thin) - small, right, moderate - small, bilateral, mild - focus/foci, tan, multiple lobes, mild - small, mild - small, severe
1596	D	Microscopic adrenal glands aorta	- within normal limits - within normal limits
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic kidneys	<ul style="list-style-type: none"> - fibrosis, bilateral, severe - corresponds to macroscopic observation (kidneys - small) - appears to be secondary to calculi.
		lacrimal glands, exorbital	<ul style="list-style-type: none"> - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, unilateral, mild - mineralization, tubular, bilateral, minimal - depletion, secretory, bilateral, severe - corresponds to macroscopic observation (lacrimal glands, exorbital - small)
		large intestine, cecum	<ul style="list-style-type: none"> - within normal limits
		large intestine, colon	<ul style="list-style-type: none"> - within normal limits
		large intestine, rectum	<ul style="list-style-type: none"> - within normal limits
		larynx	<ul style="list-style-type: none"> - within normal limits
		liver	<ul style="list-style-type: none"> - hypertrophy, hepatocyte, centrilobular, minimal
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, minimal - corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1596	D	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate corresponds to macroscopic observation (spleen - small) - within normal limits - within normal limits - depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - kidneys; fibrosis; bilateral, severe
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Macroscopic kidneys liver lymph node, inguinal pituitary gland skin, subcutis	- irregular surface, bilateral, mild - discoloration, brown, multiple lobes, moderate - within normal limits draining node for mass a, left. - enlarged, red, moderate - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 1.6 x 1.6 x 0.5 cm. - small, mild
1597	E	Microscopic thymus adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, moderate corresponds to macroscopic observation (kidneys - irregular surface) - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, unilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic	- within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild corresponds to macroscopic observation (liver - discoloration, brown) - macrophages, pigmented, minimal - necrosis, hepatocytes, centrilobular, mild corresponds to macroscopic observation (liver - discoloration, brown) - histiocytosis, alveolar, mild - not examined misidentified tissue - within normal limits - within normal limits - adenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - degeneration, axonal/myelin, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - not examined - degeneration/regeneration, myofiber, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1597	E	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small) - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1597	E	Microscopic Cause of Death	- pituitary tumor
1598	E	Macroscopic lymph node, inguinal skin, subcutis	- not identified, left, no grade draining node for mass a. - mass, tan, mass a, left inguinal area, present approximately 2.0 cm diameter.
1598	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - pheochromocytoma, benign, bilateral, primary, incidental, not cause of death - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, mild - nephropathy, chronic progressive, bilateral, mild - pyelitis, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic liver	- focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- dilatation, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- inflammation, mild
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- cyst, bilateral, minimal
		pancreas	- within normal limits
		parathyroid glands	- hyperplasia, acinar cell, focal, minimal
		pharynx	- within normal limits one of pair present

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, mild
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1598	E	Microscopic thyroid gland	- adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death
		tongue	- hyperplasia, c-cell, focal, unilateral, minimal
		trachea	- carcinoma, squamous cell, malignant, primary, fatal, positive cause of death
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- hyperplasia, simple transitional cell, minimal
		vagina	- within normal limits
		Cause of Death	- within normal limits
1599	D	Macroscopic liver	- nose/oral tumor
		lymph node, hepatic	- mass, tan, mass a, median lobe, present approximately 4.0 x 4.0 x 2.0 cm.
		pituitary gland	- within normal limits
			- draining node for mass a.
			- enlarged, red, mild

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal
			- vacuolation, focal, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- not examined
			autolysis too severe for diagnosis
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, hepatic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - carcinoma, hepatocellular, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (liver - mass a) - hypertrophy, hepatocyte, centrilobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1599	D	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - liver tumor
1600	E	Macroscopic adrenal glands	- enlarged, left, mild

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Macroscopic kidneys lymph node, axillary lymph node, mandibular pituitary gland skin, subcutis	<ul style="list-style-type: none"> - dilatation, pelvic, bilateral, mild - within normal limits draining nodes for mass b, left and mass c, right. - within normal limits draining node for mass a, right. - enlarged, mild - mass, firm, mass b, left axillary area, present corresponds to antemortem observation (mass 2) approximately 4.9 x 4.5 x 2.4 cm, tan. - mass, firm, mass c, right axillary area, present approximately 4.0 x 2.8 x 2.0 cm, tan. - mass, tan, mass a, cervical, right, present corresponds to antemortem observation (mass 1) approximately 8.7 x 8.6 x 2.6 cm. - swollen/thickened, mild
1600	E	stomach, glandular Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - necrosis, papillary, unilateral, moderate corresponds to macroscopic observation (kidneys - dilatation, pelvic) only one has appearance of pelvic dilatation (due to papillary necrosis). - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal
		lung	<ul style="list-style-type: none"> - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass c) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) collision tumor with a fibroadenoma. - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1600	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - degeneration, axonal/myelin, mild - hematopoiesis, extramedullary, increased, minimal - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - hyperplasia, c-cell, focal, unilateral, minimal - hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - stomach, glandular - swollen/thickened - mammary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1601	D	Macroscopic lymph node, inguinal	- not identified, bilateral, no grade draining node for mass a, b. may be encompassed in masses.
		mammary gland	- swollen/thickened, right inguinal area, mild
		pituitary gland	- enlarged, mild
		skin	- hair sparse, axillary, shoulder, left, mild corresponds to antemortem observation (hair sparse)
		skin, subcutis	- mass, tan, mass b, right inguinal area, present approximately 2.0 x 1.5 x 1.0 cm. - mass, ulcerated, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 2.0 x 2.0 x 1.0 cm, tan.
1601	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hydronephrosis, unilateral, mild - mineralization, pelvic, unilateral, minimal - necrosis, papillary, unilateral, mild - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic liver	- focus of cellular alteration, basophilic, moderate - necrosis, hepatocytes, centrilobular, moderate
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, multiple, primary, mortality-independent corresponds to macroscopic observation (mammary gland - swollen/thickened; skin, subcutis - mass a; skin, subcutis - mass b) slide 18, 26-1, and 26-2.
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits - within normal limits - within normal limits - hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1601	D	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, severe - adenoma, follicular cell, benign, unilateral, primary, incidental, not cause of death - cyst, follicular, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - metaplasia, squamous, mild - within normal limits - mammary tumor
1602	E	Macroscopic adrenal glands kidneys	- enlarged, right, mild - irregular surface, bilateral, mild

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1602	E	Macroscopic pituitary gland	- enlarged, red, moderate
1602	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, mild - within normal limits - within normal limits - hyperplasia, lobular, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- degeneration, axonal/myelin, minimal - exudate, nasal passage, minimal - exudate, nasal passage, minimal - inflammation, minimal - metaplasia, squamous, minimal - erosion/ulcer, moderate - exudate, nasal passage, moderate - inflammation, mild - erosion/ulcer, moderate - exudate, nasal passage, moderate - inflammation, mild - cyst, unilateral, mild - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1602	E	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - erosion/ulcer, mild - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1602	E	Microscopic uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - pituitary tumor
1603	E	Macroscopic lymph node, inguinal lymph node, mandibular pituitary gland skin, subcutis	- within normal limits draining node for mass a, right. - within normal limits draining node for mass b, right. - enlarged, red, moderate - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 8.0 cm in diameter. - mass, tan, mass b, ventral neck, present corresponds to antemortem observation (mass 2) approximately 3.5 cm in diameter.
1603	E	Microscopic adrenal glands	- atrophy, cortical, bilateral, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - cyst, unilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1603	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - mammary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1604	D	Macroscopic skin	- hair sparse, cranial, ventral thorax, moderate corresponds to antemortem observation (hair sparse)
1604	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, bilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- hyperostosis, minimal
		bone, sternum	- hyperostosis, mild
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - edema, papilla, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - fibroadenoma, benign, primary, incidental, not cause of death slide 18. - hyperplasia, lobular, minimal
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - hyperostosis, minimal - inflammation, minimal - hyperostosis, mild - hyperostosis, mild - hyperostosis, mild - cyst, unilateral, mild - fibrosis, unilateral, moderate - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1604	D	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1604	D	Microscopic Cause of Death	- kidney inflammation/necrosis
1605	E	Macroscopic clitoral glands	- enlarged, red, right, mild corresponds to antemortem observation (swelling)
		kidneys	- irregular surface, bilateral, minimal
		pituitary gland	- enlarged, red, severe
		stomach, glandular	- focus/foci, red, mucosa, mild
1605	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), mild
E - Euthanized <i>in extremis</i> D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (clitoral glands - enlarged) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cyst, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	- within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1605	E	Microscopic stomach, glandular	- erosion/ulcer, mild corresponds to macroscopic observation (stomach, glandular - focus/foci, red)
		stomach, nonglandular	- fibrosis, mild
		thymus	- erosion/ulcer, limiting ridge, mild
		thyroid gland	- depletion, lymphoid, generalized, moderate
		tongue	- within normal limits
		trachea	- hyperplasia, squamous cell, minimal
		ureters	- inflammation, subacute/chronic, minimal
		urinary bladder	- within normal limits
		uterus with cervix	- within normal limits
		vagina	- within normal limits
		Cause of Death	- pituitary tumor
1606	E	Macroscopic kidneys	- irregular surface, tan, bilateral, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Macroscopic liver lymph node, inguinal pituitary gland skin, subcutis	- focus/foci, tan, median lobe, mild - not identified, right, no grade draining node for mass a. - enlarged, red, severe - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 2.5 x 1.5 cm.
1606	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - edema, papilla, bilateral, mild - hydronephrosis, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - pyelitis, bilateral, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, mild corresponds to macroscopic observation (liver - focus/foci, tan) - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - vacuolation, focal, minimal - within normal limits - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1606	E	Microscopic spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, simple transitional cell, minimal - inflammation, minimal - within normal limits - within normal limits - pituitary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Macroscopic eyes liver lymph node, hepatic pancreas pituitary gland	- cloudy, right, mild corresponds to antemortem observation (eye discolored) - mass, tan, mass a, median lobe, present approximately 2.0 cm in diameter. - mass, tan, mass b, left lateral lobe, present approximately 3.0 x 1.9 x 0.9 cm. - mass, tan, mass c, right lateral lobe, present approximately 1.1 x 0.8 x 1.0 cm. - mass, tan, mass d, caudate lobe, present approximately 1.7 x 1.5 x 1.3 cm. - within normal limits draining node for mass a, mass b, mass c, and mass d. - enlarged, mild - enlarged, moderate
1607	S	Microscopic adrenal glands aorta	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - hyperplasia, focal medullary, unilateral, minimal - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cataract, unilateral, moderate corresponds to macroscopic observation (eyes - cloudy) - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, mild - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - inflammation, acute, unilateral, mild - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass b; liver - mass c; liver - mass d) - carcinoma, hepatocellular, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass a) - degeneration, cystic, focal, mild - focus of cellular alteration, basophilic, mild - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, panlobular, mild - histiocytosis, alveolar, minimal
		lung	- within normal limits
		lymph node, hepatic	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- hyperplasia, lobular, mild
		mammary gland	- degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, acinar cell, focal, moderate corresponds to macroscopic observation (pancreas - enlarged) - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1607	S	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Macroscopic kidneys liver lymph node, axillary pituitary gland skin, subcutis	- irregular surface, right, mild - focus/foci, white, left lateral lobe, moderate - within normal limits draining node for mass a, right. - enlarged, red, mild - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (swelling) approximately 3.0 x 2.5 x 1.0 cm. - enlarged, horn, mild
1608	D	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - mineralization, pelvic, unilateral, mild - mineralization, tubular, unilateral, mild - necrosis, papillary, unilateral, moderate - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic liver	<ul style="list-style-type: none"> - carcinoma, hepatocellular, malignant, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - focus/foci, white) - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
		lung	<ul style="list-style-type: none"> - within normal limits
		lymph node, axillary	<ul style="list-style-type: none"> - within normal limits
		lymph node, mandibular	<ul style="list-style-type: none"> - within normal limits
		lymph node, mesenteric	<ul style="list-style-type: none"> - within normal limits
		mammary gland	<ul style="list-style-type: none"> - fibroadenoma, benign, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
		nerve, sciatic	<ul style="list-style-type: none"> - within normal limits
		nose, level a	<ul style="list-style-type: none"> - within normal limits
		nose, level b	<ul style="list-style-type: none"> - within normal limits
		nose, level c	<ul style="list-style-type: none"> - within normal limits
		nose, level d	<ul style="list-style-type: none"> - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1608	D	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - enlarged) - granular cell tumor, benign, primary, incidental, not cause of death - within normal limits - pituitary tumor
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Macroscopic kidneys lymph node, inguinal pituitary gland skin, subcutis	- irregular surface, bilateral, mild - not identified, right, no grade draining node for mass a. - enlarged, red, mild - mass, tan, mass a, right anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 3.0 cm. - swollen/thickened, limiting ridge, mild
1609	D	stomach, nonglandular Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, unilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx	- within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits - within normal limits - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, acinar cell, focal, minimal - not examined - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1609	D	Microscopic pituitary gland	- hyperplasia, diffuse, pars distalis, mild corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1609	D	Microscopic thyroid gland	- carcinoma, follicular cell, malignant, unilateral, primary, incidental, not cause of death
		tongue	- within normal limits
		trachea	- within normal limits
		ureters	- within normal limits
		urinary bladder	- within normal limits
		uterus with cervix	- dilatation, gland/lumen, mild
		vagina	- within normal limits
		non-correlated macro observation	- stomach, nonglandular - swollen/thickened
		Cause of Death	- kidney inflammation/necrosis
1610	E	Macroscopic pituitary gland	- enlarged, severe
1610	E	Microscopic adrenal glands	- within normal limits
		aorta	- within normal limits
		bone marrow, femur	- within normal limits

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic liver	- hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1610	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, minimal
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- depletion, lymphoid, generalized, severe

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1610	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1611	E	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- not identified, left, no grade draining node for mass a. - enlarged, mild - mass, cystic, left inguinal area, mass a, present corresponds to antemortem observation (mass 1) mass a is approximately 6.5 cm in diameter, red, surrounded by approximately 97.0 ml. of fluid and a thin capsule.
1611	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, mild - hypertrophy, hepatocyte, centrilobular, mild - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, minimal - erythrocytosis/erythrophagocytosis, sinus, minimal - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical	- within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141

Dupont-18405-1238

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE

Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1611	E	Microscopic spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - within normal limits - mammary tumor
1612	S	Macroscopic all tissues	- within normal limits

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic kidneys	- edema, papilla, bilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
S - Scheduled necropsy			

TRADE SECRET

Study Title

**H-28548: COMBINED CHRONIC TOXICITY/ONCOGENICITY
STUDY 2-YEAR ORAL GAVAGE STUDY IN RATS**

Laboratory Project ID: DuPont-18405-1238

Volume 13 of 13

NUMBER OF PAGES IN VOLUME: 196

- TEST GUIDELINES:**
- U.S. EPA Health Effects Test Guidelines OPPTS 870.4300 Combined Chronic Toxicity/Carcinogenicity (1998)
 - OECD Guidelines for the Testing of Chemicals Section 4 (No. 453) Health Effects (2009)
 - JMAFF Japan Agricultural Chemicals Regulation Law 12 Nousan No. 8147 (2000)
 - EEC Methods for the Determination of Toxicity Method B.33 Combined Chronic/Carcinogenicity test, Directive 88/302/EC (1988)

AUTHOR: Lisa Craig, B.S.

STUDY COMPLETED ON: March 28, 2013

APPLICANT/SPONSOR: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

PERFORMING LABORATORY: MPI Research, Inc.
54943 North Main Street
Mattawan, Michigan 49071-8353
U.S.A.

WORK REQUEST NUMBER: 18405

SERVICE CODE NUMBER: 1238

MPI RESEARCH STUDY NUMBER: 125-141

Unpublished Work
Copyright ©2013 E.I. du Pont de Nemours and Company

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen	 - within normal limits - within normal limits - not examined - within normal limits - hyperplasia, focal, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1612	S	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
1613	S	Macroscopic adrenal glands kidneys	- enlarged, bilateral, mild - focus/foci, tan, right, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Macroscopic liver lymph node, hepatic lymph node, inguinal skin, subcutis	<ul style="list-style-type: none"> - focus/foci, tan, caudate lobe, mild - mass, tan, mass c, median lobe, present approximately 2.0 cm in diameter. - within normal limits draining node for mass c. - not identified, bilateral, no grade draining node for mass a, left and mass b, right. - cyst, red, left anogenital region, moderate - mass, tan, mass a, left inguinal area, present corresponds to antemortem observation (mass 1) approximately 8.0 cm in diameter. - mass, tan, mass b, right inguinal area, present corresponds to antemortem observation (mass 2) approximately 5.5 cm in diameter.
1613	S	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - corresponds to macroscopic observation (adrenal glands - enlarged) - no medulla present
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- cyst, unilateral, moderate corresponds to macroscopic observation (kidneys - focus/foci, tan) - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - mass c) - angiectasis, mild - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, mild - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	- within normal limits
		lymph node, hepatic	- not examined
			misidentified tissue
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Microscopic mammary gland	<ul style="list-style-type: none"> - adenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - cyst) - fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b) - hyperplasia, lobular, minimal - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	one of pair present
		pituitary gland	- within normal limits
			- adenoma, pars distalis, benign, primary, incidental, not cause of death
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1613	S	Microscopic salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters	- within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - dilatation, unilateral, mild
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1613	S	Microscopic urinary bladder uterus with cervix vagina non-correlated macro observation	- within normal limits - dilatation, gland/lumen, minimal - within normal limits - liver - focus/foci, tan
1614	D	Macroscopic cavity, thoracic kidneys mediastinum	- fluid, red, moderate approximately 7.5 ml. - irregular surface, bilateral, mild - enlarged, red, moderate red area continues along esophagus to thyroid glands.
1614	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1614	D	Microscopic bone, sternum brain cavity, thoracic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - hemorrhage, severe corresponds to macroscopic observation (mediastinum - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1614	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas	- within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1614	D	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	- within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, epithelial, limiting ridge, minimal
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1614	D	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1615	D	Macroscopic adrenal glands kidneys liver	- cyst, red, right, mild - enlarged, bilateral, mild - mass, tan, mass a, median lobe, present approximately 2.5 x 2.0 x 1.0 cm. - mass, tan, mass b, right lateral lobe, present approximately 0.9 x 0.6 x 0.6 cm.
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Macroscopic lung with bronchi lymph node, hepatic mammary gland	- focus/foci, tan, multiple lobes, mild - within normal limits draining node for mass a and mass b. - swollen/thickened, generalized, mild corresponds to antemortem observation (nodule) cervical region, anogenital, left and right inguinal areas most affected.
1615	D	pituitary gland stomach, glandular Microscopic adrenal glands aorta bone marrow, femur	- enlarged, red, severe - swollen/thickened, mucosa, limiting ridge, mild - angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst) - hyperplasia, focal medullary, unilateral, mild - pheochromocytoma, malignant, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Microscopic bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, focal, unilateral, mild - cardiomyopathy, mild - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - mineralization, tubular, bilateral, minimal - necrosis, papillary, unilateral, mild - nephropathy, chronic progressive, bilateral, moderate corresponds to macroscopic observation (kidneys - enlarged)
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Microscopic liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass b) - carcinoma, hepatocellular, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass a) - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, mild - vacuolation, periportal, minimal
		lung	<ul style="list-style-type: none"> - histiocytosis, alveolar, mild corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, hepatic	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	<ul style="list-style-type: none"> - hyperplasia, lobular, mild corresponds to macroscopic observation (mammary gland - swollen/thickened)
		nerve, sciatic	- degeneration, axonal/myelin, minimal
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum	- within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1615	D	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - stomach, glandular - swollen/thickened - pituitary tumor
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Macroscopic adrenal glands liver lymph node, iliac lymph node, mandibular pituitary gland skin skin, subcutis stomach, nonglandular uterus with cervix	- enlarged, left, minimal - nodule, tan, median lobe, present approximately 0.4 cm in diameter. - within normal limits draining node for mass b, bilateral. - within normal limits draining node for mass a, left. - enlarged, tan, mild - hair sparse, dorsal thoracic region, mild corresponds to antemortem observation (hair sparse) - mass, tan, mass a, left lateral neck, present corresponds to antemortem observation (swelling) approximately 4.0 x 3.0 x 1.5 cm. - swollen/thickened, limiting ridge, mild - mass, tan, mass b, body, present approximately 12.0 x 4.0 x 4.0 cm.
1616	D	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate corresponds to macroscopic observation (adrenal glands - enlarged)
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, mild - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - adenoma, hepatocellular, benign, primary, incidental, not cause of death - corresponds to macroscopic observation (liver - nodule) - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, hepatocytes, centrilobular, moderate
		lung	- histiocytosis, alveolar, minimal
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	- within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - mineralization, mild - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1616	D	Microscopic uterus with cervix vagina non-correlated macro observation Cause of Death	- schwannoma, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (uterus with cervix - mass b) - within normal limits - stomach, nonglandular - swollen/thickened - uterus tumor
1617	E	Macroscopic adrenal glands lymph node, axillary pituitary gland skin, subcutis	- cyst, clear, left, moderate cyst burst. - discoloration, red, right, mild draining node for mass a. - enlarged, red, severe - mass, tan, mass a, right axillary area, present corresponds to antemortem observation (swelling) approximately 5.0 x 3.5 x 2.0 cm.

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1617	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, moderate corresponds to macroscopic observation (adrenal glands - cyst)
		aorta	- within normal limits
		bone marrow, femur	- within normal limits
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- compression, ventral (pituitary tumor), moderate
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1617	E	Microscopic kidneys	- mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, minimal
		lung	- within normal limits
		lymph node, axillary	- erythrocytosis/erythrophagocytosis, sinus, mild corresponds to macroscopic observation (lymph node, axillary - discoloration, red)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1617	E	Microscopic mammary gland	- fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1617	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1617	E	Microscopic vagina Cause of Death	- within normal limits - pituitary tumor
1618	S	Macroscopic all tissues	- within normal limits
1618	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1618	S	Microscopic eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung	- within normal limits one of pair present - within normal limits - hyperplasia, focal, unilateral, minimal - cardiomyopathy, minimal - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - degeneration, cystic, focal, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1618	S	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual	- within normal limits - within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1618	S	Microscopic skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1619	E	Macroscopic lymph node, axillary lymph node, inguinal skin, subcutis	- not identified, right, no grade draining node for mass a. - not identified, left, no grade draining node for mass b. - mass, tan, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 6.0 x 6.0 x 2.5 cm. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 8.5 x 7.5 x 4.0 cm, tan. - fluid, clear, frothy, mild
1619	E	trachea Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1619	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1619	E	Microscopic lung	- fibrosis, minimal - histiocytosis, alveolar, minimal - inflammation, acute, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, multiple, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b)
		nerve, sciatic	- hyperplasia, lobular, mild
		nose, level a	- degeneration, axonal/myelin, minimal
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- adenoma, islet cell, benign, primary, incidental, not cause of death
		parathyroid glands	- not examined

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1619	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1619	E	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1620	E	Macroscopic lymph node, iliac skin, subcutis uterus with cervix	- within normal limits draining node for mass a, bilateral. - mass, ulcerated, mass a, anogenital region, present corresponds to antemortem observation (mass 1) approximately 4.0 cm in diameter, tan. - cyst, clear, body, moderate - enlarged, body, mild
1620	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1620	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain cavity, abdominal esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - sarcoma, stromal, malignant, secondary corresponds to macroscopic observation (uterus with cervix - cyst) adjacent to uterus. - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1620	E	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, iliac lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b	- mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - leukocytosis, sinusoidal, minimal - necrosis, focal, moderate - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1620	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - not examined - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1620	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, cervical fibromuscular, moderate corresponds to macroscopic observation (uterus with cervix - enlarged) - sarcoma, stromal, malignant, primary, fatal, positive cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, fibromuscular, moderate - uterus tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1621	S	Macroscopic liver lymph node, hepatic	- mass, red, mass a, median lobe, present approximately 1.0 x 0.4 x 0.4 cm. - not identified, no grade draining node for mass a.
1621	S	pituitary gland Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- cyst, red, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1621	S	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	<ul style="list-style-type: none"> - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, hepatocellular, benign, primary, incidental, not cause of death corresponds to macroscopic observation (liver - mass a) - degeneration, cystic, focal, minimal - focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1621	S	Microscopic lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular	- histiocytosis, alveolar, minimal - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, islet cell, benign, primary, incidental, not cause of death - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - cyst) - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1621	S	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1621	S	Microscopic uterus with cervix vagina	- within normal limits - within normal limits
1622	D	Macroscopic liver lung with bronchi stomach, nonglandular	- focus/foci, tan, median lobe, left lateral lobe, mild - focus/foci, tan, multiple lobes, mild - swollen/thickened, limiting ridge, mild
1622	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal cortical, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1622	D	Microscopic esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - necrosis, papillary, bilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1622	D	Microscopic liver	- adenoma, hepatocellular, benign, multiple, primary, incidental, not cause of death corresponds to macroscopic observation (liver - focus/foci, tan)
		lung	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, mild corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1622	D	Microscopic parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- not examined - within normal limits - hyperplasia, focal, pars distalis, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1622	D	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - stomach, nonglandular - swollen/thickened - kidney inflammation/necrosis
1623	S	Macroscopic adrenal glands lung with bronchi lymph node, axillary lymph node, inguinal ovaries pituitary gland	- enlarged, right, moderate - focus/foci, white, multiple lobes, mild - within normal limits draining node for mass a, right. - within normal limits draining node for mass b, right. - cyst, clear, left, mild - enlarged, mild

S - Scheduled necropsy
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1623	S	Macroscopic skin	- nodule, tan, dorsal lumbar region, present corresponds to antemortem observation (nodule) approximately 0.4 cm in diameter.
		skin, subcutis	- mass, tan, mass a, right axillary area, present approximately 2.2 x 1.5 x 1.0 cm.
			- mass, tan, mass b, right lateral abdomen, present approximately 1.2 cm in diameter.
			- swollen/thickened, moderate
1623	S	stomach, glandular Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, severe corresponds to macroscopic observation (adrenal glands - enlarged)
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- hyperplasia, granulocytic, minimal
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1623	S	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- within normal limits - within normal limits - within normal limits - within normal limits - degeneration/atrophy, retina, unilateral, mild - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - focus of cellular alteration, basophilic, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1623	S	Microscopic lung lymph node, axillary lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, moderate - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, mild corresponds to macroscopic observation (ovaries - cyst) - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1623	S	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- hyperplasia, acinar cell, focal, mild - not examined - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - keratoacanthoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin - nodule) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1623	S	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina non-correlated macro observation	- within normal limits - leiomyoma, benign, primary, incidental, not cause of death - cyst, keratin, moderate corresponds to macroscopic observation (stomach, glandular - swollen/thickened) - depletion, lymphoid, generalized, moderate - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - lung with bronchi - focus/foci, white
1624	E	Macroscopic lymph node, axillary	- within normal limits draining node for mass b, right.

S - Scheduled necropsy
E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1624	E	Macroscopic lymph node, mandibular pituitary gland skin skin, subcutis	- within normal limits draining node for mass a, right. - enlarged, red, severe - hair sparse, generalized, mild - mass, tan, mass a, cervical, present corresponds to antemortem observation (mass 1) approximately 2.0 cm in diameter, right. - mass, tan, mass b, right axillary area, present corresponds to antemortem observation (nodule) approximately 3.5 cm in diameter.
1624	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1624	E	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver	- compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - mineralization, tubular, unilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1624	E	Microscopic lung lymph node, axillary lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1624	E	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular	- within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1624	E	Microscopic stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1625	D	Macroscopic adipose tissue cavity, abdominal	- swollen/thickened, mild near hilus of liver. small, round, orange granules are on the surface. - fluid, red, mild approximately 2.4 ml.

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1625	D	Macroscopic lymph node, mandibular skin	- enlarged, red, mild - hair sparse, left lateral neck, moderate corresponds to antemortem observation (hair sparse)
1625	D	spleen Microscopic adrenal glands aorta bile duct, extrahepatic bone marrow, femur bone marrow, sternum bone, femur bone, sternum	- enlarged, moderate - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - calculus/calculi, moderate bile stained. - dilatation, moderate corresponds to macroscopic observation (adipose tissue - swollen/thickened) - bacterial colonies, mild - hyperplasia, granulocytic, mild - proliferation, fibro-osseous, moderate - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1625	D	Microscopic brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- bacterial colonies, minimal - inflammation, embolic, minimal - within normal limits - within normal limits - within normal limits - not examined autolysis too severe for diagnosis - within normal limits - within normal limits - bacterial colonies, mild - inflammation, moderate - thrombus, moderate left ventricle. - within normal limits - bacterial colonies, unilateral, minimal - edema, papilla, bilateral, minimal - inflammation, embolic, unilateral, minimal - mineralization, pelvic, unilateral, minimal - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1625	D	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mediastinal lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d	 - hypertrophy/hyperplasia, goblet cell, moderate - hypertrophy/hyperplasia, goblet cell, moderate - hypertrophy/hyperplasia, goblet cell, moderate - within normal limits - fibrosis, severe - inflammation, chronic-active, moderate - histiocytosis, alveolar, minimal - hyperplasia, lymphocyte/plasmacyte, medulla, mild corresponds to macroscopic observation (lymph node, mandibular - enlarged) - hyperplasia, lymphocyte/plasmacyte, medulla, mild slide 14. - hyperplasia, lymphocyte/plasmacyte, medulla, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1625	D	Microscopic ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum	- within normal limits - within normal limits - adenoma, islet cell, benign, primary, incidental, not cause of death slide 26-1. - bacterial colonies, severe within blood vessels. - within normal limits one of pair present - within normal limits - cyst, mild - within normal limits - edema, mild - within normal limits - within normal limits - alopecia/hypotrichosis, moderate corresponds to macroscopic observation (skin - hair sparse) - hypertrophy/hyperplasia, goblet cell, mild - hypertrophy/hyperplasia, goblet cell, moderate
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1625	D	Microscopic small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hypertrophy/hyperplasia, goblet cell, moderate - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, moderate corresponds to macroscopic observation (spleen - enlarged) - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - erosion/ulcer, moderate - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - inflammation/septicemia
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Macroscopic liver lung with bronchi lymph node, axillary lymph node, inguinal ovaries pituitary gland skin, subcutis stomach, glandular stomach, nonglandular thymus	- focus/foci, tan, median lobe, mild - focus/foci, tan, multiple lobes, mild - within normal limits draining node for mass a and mass b, right. - within normal limits draining node for mass c, right. - cyst, clear, right, mild - enlarged, moderate - mass, tan, mass b, right axillary area, present approximately 2.0 cm in diameter. - mass, tan, mass c, right anogenital region, present approximately 1.5 cm in diameter. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 2.0 x 1.2 cm, tan. - focus/foci, red, mucosa, mild - swollen/thickened, limiting ridge, mild - small, severe

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, bilateral, minimal - hyperplasia, focal medullary, unilateral, minimal - vacuolation, focal, unilateral, minimal
		aorta	- within normal limits
		bone marrow, femur	- hyperplasia, granulocytic, mild
		bone marrow, sternum	- within normal limits
		bone, femur	- within normal limits
		bone, sternum	- within normal limits
		brain	- within normal limits
		esophagus	- within normal limits
		eyes	- within normal limits
		eyes, optic nerves	- within normal limits
		eyes, retina	- within normal limits
		galt	- within normal limits
		harderian glands	- within normal limits
		heart	- cardiomyopathy, minimal
		joint, tibiofemoral	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Microscopic kidneys	<ul style="list-style-type: none"> - edema, papilla, unilateral, minimal - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - degeneration, cystic, focal, minimal - focus of cellular alteration, eosinophilic, moderate - corresponds to macroscopic observation (liver - focus/foci, tan) - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, mild
		lung	<ul style="list-style-type: none"> - infiltration, mononuclear cell, minimal - histiocytosis, alveolar, mild - corresponds to macroscopic observation (lung with bronchi - focus/foci, tan)
		lymph node, axillary	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Microscopic lymph node, inguinal lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts	- within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - fibroadenoma, benign, multiple, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass c) - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - cyst, unilateral, minimal corresponds to macroscopic observation (ovaries - cyst) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Microscopic pancreas	- atrophy, acinar, minimal - fibrosis, minimal
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1626	E	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - hematopoiesis, extramedullary, increased, mild - erosion/ulcer, mild corresponds to macroscopic observation (stomach, glandular - focus/foci, red) - hyperplasia, epithelial, limiting ridge, moderate corresponds to macroscopic observation (stomach, nonglandular - swollen/thickened) - depletion, lymphoid, generalized, severe corresponds to macroscopic observation (thymus - small) - hyperplasia, c-cell, focal, unilateral, mild - hyperplasia, squamous cell, mild - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits - mammary tumor

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1627	E	Macroscopic lymph node, axillary skin, subcutis	- within normal limits draining node for mass a, right. - mass, ulcerated, mass a, right axillary area, present corresponds to antemortem observation (mass 1 scabbed area) approximately 3.0 cm in diameter, tan.
1627	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - hyperplasia, granulocytic, minimal - hyperplasia, granulocytic, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1627	E	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary	- within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - hydronephrosis, unilateral, mild - hyperplasia, transitional cell, unilateral, minimal - mineralization, pelvic, unilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, minimal - histiocytosis, alveolar, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1627	E	Microscopic lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid	- within normal limits - within normal limits - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1627	E	Microscopic salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1627	E	Microscopic vagina Cause of Death	- within normal limits - mammary tumor
1628	S	Macroscopic uterus with cervix	- enlarged, horn, mild
1628	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in RatsIndividual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1628	S	Microscopic galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular	<ul style="list-style-type: none">- within normal limits- within normal limits- within normal limits- within normal limits- dilatation, tubular, unilateral, minimal- mineralization, tubular, bilateral, minimal- nephropathy, chronic progressive, bilateral, mild- within normal limits- within normal limits- within normal limits- within normal limits- within normal limits- focus of cellular alteration, basophilic, mild- focus of cellular alteration, clear, minimal- hyperplasia, bile duct, minimal- hypertrophy, hepatocyte, centrilobular, minimal- infiltration, mononuclear cell, minimal- histiocytosis, alveolar, minimal- within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1628	S	Microscopic lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris	- within normal limits - hyperplasia, lobular, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, sex-cord/stromal, bilateral, mild - within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1628	S	Microscopic skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, minimal - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - enlarged) - within normal limits

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1629	D	Macroscopic kidneys lymph node, iliac lymph node, inguinal skin, subcutis uterus with cervix	- irregular surface, red, bilateral, mild - within normal limits draining node for mass b, right. - within normal limits draining node for mass a, left. - mass, tan, mass a, left inguinal area, present approximately 1.0 x 1.0 x 0.5 cm. - mass, tan, mass b, horn, present approximately 4.0 x 3.0 x 1.5 cm.
1629	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus	- angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1629	D	Microscopic eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, moderate - nephropathy, chronic progressive, bilateral, mild corresponds to macroscopic observation (kidneys - irregular surface) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1629	D	Microscopic liver	- hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, iliac	- within normal limits
		lymph node, inguinal	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- fibroadenoma, benign, primary, incidental, not cause of death corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1629	D	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1629	D	Microscopic tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hyperplasia, squamous cell, moderate - inflammation, subacute/chronic, mild - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death corresponds to macroscopic observation (uterus with cervix - mass b) - within normal limits - kidney inflammation/necrosis
1630	D	Macroscopic lymph node, axillary ovaries pituitary gland	- within normal limits draining node for mass a, left. - cyst, clear, right, mild - enlarged, red, moderate
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1630	D	Macroscopic skin, subcutis	- mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 3.0 cm in diameter.
1630	D	uterus with cervix Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt	- cyst, clear, horn, mild - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), minimal - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1630	D	Microscopic harderian glands heart joint, tibiofemoral kidneys lacrimial glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - cardiomyopathy, minimal - within normal limits - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - vacuolation, periportal, minimal - histiocytosis, alveolar, mild - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1630	D	Microscopic mammary gland	- adenocarcinoma, malignant, primary, incidental, not cause of death slide 18. - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1630	D	Microscopic salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea	- within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1630	D	Microscopic ureters urinary bladder uterus with cervix vagina non-correlated macro observation Cause of Death	- within normal limits - within normal limits - dilatation, gland/lumen, mild corresponds to macroscopic observation (uterus with cervix - cyst) - within normal limits - ovaries - cyst - pituitary tumor
1631	S	Macroscopic all tissues	- within normal limits
1631	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits

S - Scheduled necropsy
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1631	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mineralization, pelvic, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1631	S	Microscopic liver	- focus of cellular alteration, basophilic, minimal - focus of cellular alteration, eosinophilic, minimal - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal
		lung	- within normal limits
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	- hyperplasia, lobular, minimal
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- within normal limits one of pair present
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1631	S	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, mild

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1631	S	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits
1632	S	Macroscopic skin	- hair sparse, left lateral neck, right lateral neck, mild corresponds to antemortem observation (hair sparse)
1632	S	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1632	S	Microscopic bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, mild - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1632	S	Microscopic large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands	- within normal limits - within normal limits - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, mild - degeneration, axonal/myelin, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - hyperplasia, acinar cell, focal, mild - within normal limits one of pair present
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1632	S	Microscopic pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus	- within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - alopecia/hypotrichosis, mild corresponds to macroscopic observation (skin - hair sparse) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1632	S	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hyperplasia, cervical fibromuscular, mild - within normal limits
1633	S	Macroscopic lymph node, inguinal pituitary gland skin, subcutis	- not identified, right, no grade draining node for mass a. - enlarged, red, mild - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 4.0 x 3.0 x 2.0 cm.
1633	S	Microscopic adrenal glands	- angiectasis/cystic degeneration, focal cortical, unilateral, mild - hyperplasia, focal cortical, unilateral, minimal
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1633	S	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1633	S	Microscopic kidneys	<ul style="list-style-type: none"> - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, mild - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - necrosis, papillary, bilateral, moderate - nephropathy, chronic progressive, bilateral, mild
		lacrimal glands, exorbital	- within normal limits
		large intestine, cecum	- within normal limits
		large intestine, colon	- within normal limits
		large intestine, rectum	- within normal limits
		larynx	- within normal limits
		liver	<ul style="list-style-type: none"> - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- within normal limits
		lymph node, mesenteric	- within normal limits
		mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- degeneration, axonal/myelin, minimal

S - Scheduled necropsy

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1633	S	Microscopic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin	- inflammation, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - atrophy, acinar, minimal - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - degeneration/necrosis, myofiber, minimal - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1633	S	Microscopic small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - hyperplasia, epithelial cell, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - hyperplasia, squamous cell, minimal - within normal limits
S - Scheduled necropsy			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1634	E	Macroscopic lymph node, inguinal ovaries pituitary gland skin, subcutis	<ul style="list-style-type: none"> - not identified, bilateral, no grade draining node for mass a, left and mass b, right. - cyst, red, left, moderate - enlarged, red, mild - mass, tan, mass a, left anogenital region, present corresponds to antemortem observation (mass 1) approximately 5.0 x 5.0 x 3.0 cm. - mass, ulcerated, mass b, right anogenital region, present corresponds to antemortem observation (mass 2) approximately 3.5 cm in diameter, tan.
1634	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate one medulla present - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, minimal - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1634	E	Microscopic bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal - within normal limits - hyperplasia, transitional cell, bilateral, minimal - nephropathy, chronic progressive, bilateral, minimal - pyelitis, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1634	E	Microscopic liver	- hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, mild - necrosis, focal, minimal
		lung	- histiocytosis, alveolar, minimal
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass b) - fibroadenoma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - hyperplasia, lobular, mild
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- hemangiosarcoma, malignant, unilateral, primary, incidental, not cause of death corresponds to macroscopic observation (ovaries - cyst)
		oviducts	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1634	E	Microscopic pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic	- within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1634	E	Microscopic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - mammary tumor
1635	E	Macroscopic lymph node, inguinal	- not identified, right, no grade draining node for mass a.

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1635	E	Macroscopic skin, subcutis	- mass, ulcerated, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 6.5 cm in diameter, tan.
1635	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart	- within normal limits - within normal limits - hyperplasia, granulocytic, mild - hyperplasia, granulocytic, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - cardiomyopathy, minimal

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1635	E	Microscopic joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland	- within normal limits - dilatation, tubular, bilateral, mild - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - hypertrophy, hepatocyte, centrilobular, mild - necrosis, hepatocytes, centrilobular, moderate - within normal limits - within normal limits - within normal limits - within normal limits
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1635	E	Microscopic nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin skin, subcutis small intestine, duodenum	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibroma, benign, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a) - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1635	E	Microscopic small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - fibrosarcoma/fibroma

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Macroscopic liver lymph node, axillary lymph node, iliac lymph node, inguinal pituitary gland	- focus/foci, tan, multifocal, multiple lobes, moderate - within normal limits left is draining node for mass a. right is draining node for mass c. - within normal limits right and left are draining nodes for mass e. - within normal limits left is draining node for mass b. right is draining node for mass d. - enlarged, tan, mild
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, tan, mass a, left axillary area, present corresponds to antemortem observation (mass 1) approximately 3.5 x 3.5 x 1.7 cm. - mass, tan, mass c, right axillary area, present corresponds to antemortem observation (mass 3) approximately 4.8 x 3.7 x 1.8 cm. - mass, tan, mass d, right inguinal area, present corresponds to antemortem observation (swelling) approximately 1.8 x 1.0 x 0.6 cm. - mass, tan, mass e, anogenital region, present corresponds to antemortem observation (swelling) approximately 5.5 x 4.0 x 2.0 cm. - mass, ulcerated, mass b, left inguinal area, present corresponds to antemortem observation (mass 2) approximately 4.5 x 3.5 x 2.0 cm and tan in color.
1636	E	Microscopic adrenal glands	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, unilateral, minimal - hyperplasia, focal medullary, bilateral, mild

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Microscopic aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - mineralization, pelvic, bilateral, minimal - mineralization, tubular, bilateral, minimal - nephropathy, chronic progressive, bilateral, mild - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, iliac lymph node, inguinal lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - within normal limits - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - necrosis, hepatocytes, centrilobular, moderate corresponds to macroscopic observation (liver - focus/foci, tan) - adenocarcinoma, malignant, secondary - histiocytosis, alveolar, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Microscopic mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass b; skin, subcutis - mass d) - fibroadenoma, benign, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass c; skin, subcutis - mass e) - hyperplasia, lobular, minimal
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- within normal limits
		nose, level d	- within normal limits
		ovaries	- within normal limits
		oviducts	- within normal limits
		pancreas	- within normal limits
		parathyroid glands	- not examined
		pharynx	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Microscopic pituitary gland	- adenoma, pars distalis, benign, primary, incidental, not cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- hematopoiesis, extramedullary, increased, moderate
		stomach, glandular	- within normal limits
		stomach, nonglandular	- within normal limits
		thymus	- not examined

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1636	E	Microscopic thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, gland/lumen, minimal - granular cell tumor, benign, primary, incidental, not cause of death - mammary tumor
1637	E	Macroscopic lymph node, axillary lymph node, inguinal lymph node, mandibular pituitary gland	- within normal limits draining node for mass e, right. - not identified, right, no grade draining node for mass a and mass b. - within normal limits draining node for mass c, right and mass d, left. - enlarged, red, severe

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Macroscopic skin, subcutis	<ul style="list-style-type: none"> - mass, red, mass d, ventral neck, left, present corresponds to antemortem observation (nodule) approximately 2.0 x 2.0 x 1.0 cm. - mass, tan, mass a, right inguinal area, present corresponds to antemortem observation (mass 1) approximately 7.0 x 6.5 x 2.5 cm. - mass, tan, mass b, right anogenital region, present approximately 4.0 x 2.5 x 2.0 cm. - mass, tan, mass c, ventral neck, right, present corresponds to antemortem observation (nodule) approximately 3.0 x 2.5 x 1.0 cm. - mass, tan, mass e, right axillary area, present corresponds to antemortem observation (swelling) approximately 3.0 x 1.5 x 1.0 cm.
1637	E	Microscopic adrenal glands aorta	<ul style="list-style-type: none"> - angiectasis/cystic degeneration, focal cortical, bilateral, moderate - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital large intestine, cecum	- within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), moderate - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, mild - mineralization, pelvic, bilateral, minimal - necrosis, papillary, bilateral, moderate - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Microscopic large intestine, colon large intestine, rectum larynx liver lung lymph node, axillary lymph node, mandibular lymph node, mesenteric	- within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - necrosis, focal, minimal - vacuolation, median cleft, mild - histiocytosis, alveolar, minimal - not examined misidentified tissue - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Microscopic mammary gland	<ul style="list-style-type: none"> - adenocarcinoma, malignant, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass b; skin, subcutis - mass d) - fibroadenoma, benign, multiple, primary, mortality-independent - corresponds to macroscopic observation (skin, subcutis - mass a; skin, subcutis - mass c; skin, subcutis - mass e) - hyperplasia, lobular, mild
		nerve, sciatic	- within normal limits
		nose, level a	- within normal limits
		nose, level b	- within normal limits
		nose, level c	- foreign material, mild plant.
		nose, level d	- foreign material, mild plant.
		ovaries	- cyst, unilateral, mild
		oviducts	- within normal limits
		pancreas	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Microscopic parathyroid glands	- within normal limits one of pair present
		pharynx	- within normal limits
		pituitary gland	- adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged)
		salivary gland, mandibular	- within normal limits
		salivary gland, parotid	- within normal limits
		salivary gland, sublingual	- within normal limits
		skeletal muscle, biceps femoris	- within normal limits
		skin	- within normal limits
		small intestine, duodenum	- within normal limits
		small intestine, ileum	- within normal limits
		small intestine, jejunum	- within normal limits
		spinal cord, cervical	- within normal limits
		spinal cord, lumbar	- within normal limits
		spinal cord, thoracic	- within normal limits
		spleen	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1637	E	Microscopic stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor
1638	E	Macroscopic kidneys lung with bronchi lymph node, iliac	- focus/foci, white, left, mild - focus/foci, black, multiple lobes, moderate - enlarged, left, mild draining node for mass a, bilateral.
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1638	E	Macroscopic skin, subcutis	- mass, ulcerated, mass a, anogenital region, bilateral, present corresponds to antemortem observation (mass 2 mass 1) approximately 12.2 x 6.5 x 4.5 cm, tan with some fluid present.
1638	E	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum bone, tibia brain cavity, abdominal esophagus eyes	- angiectasis/cystic degeneration, focal cortical, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - proliferation, fibro-osseous, mild - within normal limits - adenocarcinoma, malignant, secondary corresponds to macroscopic observation (lymph node, iliac - enlarged) - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1638	E	Microscopic eyes, optic nerves eyes, retina gall harderian glands heart joint, tibiofemoral kidneys lacrima glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - adenocarcinoma, malignant, unilateral, secondary corresponds to macroscopic observation (kidneys - focus/foci, white) from mammary tumor. - edema, papilla, bilateral, minimal - hyperplasia, transitional cell, bilateral, minimal - mineralization, pelvic, bilateral, mild - nephropathy, chronic progressive, bilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1638	E	Microscopic liver	<ul style="list-style-type: none"> - hematopoiesis, extramedullary, minimal - hyperplasia, bile duct, minimal - hypertrophy, hepatocyte, centrilobular, minimal - necrosis, focal, mild
		lung	<ul style="list-style-type: none"> - necrosis, individual hepatocyte, mild - adenocarcinoma, malignant, secondary corresponds to macroscopic observation (lung with bronchi - focus/foci, black) from mammary tumor. - hemorrhage, mild - macrophages, pigmented alveolar, mild
		lymph node, iliac	- within normal limits
		lymph node, mandibular	- erythrocytosis/erythrophagocytosis, sinus, minimal
		lymph node, mesenteric	- within normal limits
		mammary gland	- adenocarcinoma, malignant, primary, mortality-independent corresponds to macroscopic observation (skin, subcutis - mass a)
		nerve, sciatic	- degeneration, axonal/myelin, minimal
		nose, level a	- within normal limits
		nose, level b	- within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1638	E	Microscopic nose, level c nose, level d ovaries oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - cyst, bilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - adenoma, pars distalis, benign, primary, incidental, not cause of death - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1638	E	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - hematopoiesis, extramedullary, increased, mild - within normal limits - hyperplasia, epithelial, limiting ridge, minimal - depletion, lymphoid, generalized, moderate - hyperplasia, epithelial cell, minimal - adenoma, c-cell, benign, unilateral, primary, incidental, not cause of death - hyperplasia, follicular cell, unilateral, mild - within normal limits - within normal limits - within normal limits - within normal limits - polyp, stromal, benign, primary, incidental, not cause of death - within normal limits - mammary tumor
E - Euthanized <i>in extremis</i>			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats**Individual Animal Listing - FEMALE**
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u>			
1639	D	Macroscopic all tissues	- within normal limits
1639	D	Microscopic adrenal glands aorta bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1639	D	Microscopic kidneys lacrimal glands, exorbital large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- cyst, unilateral, minimal - mineralization, tubular, unilateral, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1639	D	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar spinal cord, thoracic spleen stomach, glandular stomach, nonglandular	 - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits
D - Died on Study			

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1639	D	Microscopic thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dosing injury
1640	E	Macroscopic adipose tissue	- focus/foci, yellow, mild white adipose tissue cranial to kidney on right side.
1640	E	pituitary gland Microscopic adrenal glands aorta	- enlarged, red, moderate - angiectasis/cystic degeneration, focal cortical, bilateral, mild - within normal limits

E - Euthanized *in extremis*
D - Died on Study

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1640	E	Microscopic bone marrow, femur bone marrow, sternum bone, femur bone, sternum brain esophagus eyes eyes, optic nerves eyes, retina galt harderian glands heart joint, tibiofemoral kidneys lacrimal glands, exorbital	- within normal limits - within normal limits - within normal limits - within normal limits - compression, ventral (pituitary tumor), mild - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - dilatation, tubular, bilateral, minimal - edema, papilla, unilateral, minimal - mineralization, pelvic, bilateral, minimal - necrosis, papillary, unilateral, severe - nephropathy, chronic progressive, bilateral, mild - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1640	E	Microscopic large intestine, cecum large intestine, colon large intestine, rectum larynx liver lung lymph node, mandibular lymph node, mesenteric mammary gland mesentery/peritoneum nerve, sciatic nose, level a nose, level b nose, level c nose, level d ovaries	- within normal limits - within normal limits - within normal limits - within normal limits - hypertrophy, hepatocyte, centrilobular, minimal - infiltration, mononuclear cell, minimal - within normal limits - within normal limits - within normal limits - hyperplasia, lobular, minimal - necrosis, fat, mild corresponds to macroscopic observation (adipose tissue - focus/foci, yellow) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1640	E	Microscopic oviducts pancreas parathyroid glands pharynx pituitary gland salivary gland, mandibular salivary gland, parotid salivary gland, sublingual skeletal muscle, biceps femoris skin small intestine, duodenum small intestine, ileum small intestine, jejunum spinal cord, cervical spinal cord, lumbar	- within normal limits - within normal limits - within normal limits one of pair present - within normal limits - adenoma, pars distalis, benign, primary, fatal, positive cause of death corresponds to macroscopic observation (pituitary gland - enlarged) - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits

E - Euthanized *in extremis*

MPI Research Study Number 125-141
Dupont-18405-1238
H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Individual Animal Listing - FEMALE
Terminal

Group, Animal Number	Fate	Tissue	Observations
<u>500 mg/kg/day</u> 1640	E	Microscopic spinal cord, thoracic spleen stomach, glandular stomach, nonglandular thymus thyroid gland tongue trachea ureters urinary bladder uterus with cervix vagina Cause of Death	- within normal limits - within normal limits - within normal limits - within normal limits - depletion, lymphoid, generalized, severe - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - within normal limits - pituitary tumor

E - Euthanized *in extremis*

Appendix K
Section 2
Pathology Peer Review Statement

TRADE SECRET

Unpublished Work
Copyright ©2013 E.I. du Pont de Nemours and Company

STUDY TITLE: Anatomic Pathology Peer Review Report for
H-28548: Combined Chronic Toxicity/Oncogenicity Study
2-Year Oral Gavage Study in Rats

AUTHOR: Steven R. Frame, D.V.M., Ph.D., Diplomate ACVP

ANATOMIC PATHOLOGY PEER

REVIEW REPORT COMPLETED: March 25, 2013

PERFORMING LABORATORY: E.I. du Pont de Nemours and Company
DuPont Haskell Global Centers for
Health & Environmental Sciences
P.O. Box 50
Newark, Delaware 19714
U.S.A.

TESTING FACILITY: MPI Research, Inc.
54943 North Main Street
Mattawan, Michigan 49071-9399
U.S.A.

LABORATORY PROJECT ID: DuPont-18405-1238

WORK REQUEST NUMBER: 18405

SERVICE CODE NUMBER: 1238

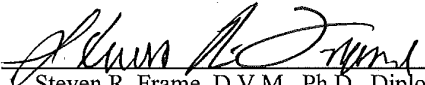
SPONSOR: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

TESTING FACILITY STUDY 125-141
NUMBER:

GOOD LABORATORY PRACTICE COMPLIANCE STATEMENT

The work performed at DuPont Haskell was conducted in compliance with U.S. EPA TSCA (40 CFR part 792) Good Laboratory Practice Standards, which are compatible with current OECD Good Laboratory Practices.

Sponsor: E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898
U.S.A.

Principal Investigator:  25 March 2013
Steven R. Frame, D.V.M., Ph.D., Diplomate ACVP
Senior Research Fellow and Manager
E.I. du Pont de Nemours and Company
Date

Sponsor: _____
Sponsor Representative
Date

QUALITY ASSURANCE STATEMENT

MPI Research Number 125-141
Work Request Number: 18405
Service Code Number: 1238

Key inspections for the above referenced study's Peer Pathology Report were completed by the Quality Assurance Unit of DuPont Haskell and the findings were submitted on the following dates:

<i>Audit Dates</i>	<i>Date Reported to:</i>			
	<i>Principal Investigator (PI)</i>	<i>PI Management</i>	<i>Study Director (SD)</i>	<i>SD Management</i>
<u>Report/Records:</u> March 15, 17, 2013	March 18, 2013	March 18, 2013	March 18, 2013	March 19, 2013

Reported by:

Robert C Rhea

Robert C. Rhea RQAP-GLP
Quality Assurance Auditor

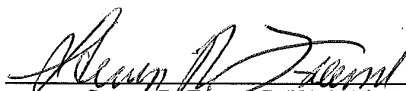
25-MAR-2013

Date

CERTIFICATION

I, the undersigned, declare that these results provide accurate data obtained from this study.

Issued by
Principal Investigator:



Steven R. Frame, D.V.M., Ph.D., DACVP
Senior Research Fellow and Manager

25 March 2013

Date

SUMMARY

Gross observations, organ weights, microscopic findings, and the pathology report of this 2-year oral gavage study in rats with H-28548 were peer reviewed according to the DuPont Haskell Recommendations for Tissue Examination in Pathology Peer Reviews. The peer review pathologist is in agreement with the conclusions of the study pathologist as given in the pathology report.

INTRODUCTION

This report documents the peer review of pathology data, including gross observations, organ weights, and microscopic findings for this study.

METHODS

A peer review of the gross observations, organ weights, microscopic findings, and the pathology report for DuPont-18405-1238 was conducted for male and female Crl:CD(SD) rats by a peer review pathologist. The peer review was conducted at MPI Research, Inc., 54943 North Main Street, Mattawan, Michigan, U.S.A. 49071-9399 and at DuPont Haskell Global Centers for Health & Environmental Sciences, P.O. Box 50, Newark, Delaware, U.S.A. 19714.

Twelve-Month Interim

For the twelve-month interim sacrifice, sections of all available tissues from the following animals in the male and female high-dose groups (Groups 4 and 5, respectively) were reviewed microscopically:

Males: 1241, 1245, and 1250

Females: 1561, 1565, and 1570

In addition, liver and testes from male rats; liver and kidneys from females rats; and all neoplasms in all male and female groups were examined microscopically.

Terminal (or 24-Month Terminal)

For the terminal sacrifice, sections of all available tissues from the following animals were reviewed microscopically:

Terminal Sacrifice		
Male Groups:	1	4
Animal Number(s):	1011	1256
	1029	1269
	1037	1275
	1050	1294
	1051	1298
	1057	1305
	1058	1316
Female Groups:	1	5
Animal Number(s):	1323	1591
	1336	1610
	1342	1619
	1358	1625
	1364	1628
	1384	1633
	1392	1634

In addition, liver, pancreas, and testes in males, and liver, kidneys, stomach, tongue, pancreas, and lungs in females were examined microscopically from all groups as potential target organs or to clarify findings in the high dose groups. All neoplasms in all two-year groups were also examined.

For both the 12-month interim and terminal sacrifice, other selected tissues were examined as necessary by the reviewing pathologist to clarify diagnostic terms and confirm microscopic findings. The pathology report and the summary incidence tables for gross findings, organ weight changes, and microscopic findings were also reviewed.

RESULTS

The quality of the histopathology sections and accountability of tissues for examination were good, and there was good agreement between the study pathologist and peer review pathologist regarding severity grading and diagnoses of lesions. Terminology and diagnoses were agreed upon by the study pathologist and the peer review pathologist for all the organs, and this agreement is reflected in the final report.

CONCLUSIONS

A peer review of the gross observations, organ weights, microscopic findings, and the pathology report for DuPont-18405-1238 was conducted according to DuPont Haskell Recommendations for Tissue Examination in Pathology Peer Reviews. The peer review pathologist is in agreement with the interpretations and conclusions of the study pathologist as given in the pathology report.

RECORDS AND SAMPLE STORAGE

For the work conducted at DuPont Haskell, the anatomic pathology peer review report will be retained at DuPont Haskell, Newark, Delaware or Iron Mountain Records Management, Wilmington, Delaware.

Appendix L
MPI Research Computer Systems

MPI Research Computer Systems

The computer systems used during the conduct of this study are presented in the following table.

MPI Research Computer Systems	
Provantis™ v8.0:	Client-server, Oracle-based system used for electronic documentation and data management from compound receipt through reporting.
Siemens Environmental Monitoring vMPI1 and Niagara Framework® Software System v2.3:	Environmental monitoring, alarming, and reporting applications.
MPI Research ExyLIMS v3.0:	A comprehensive laboratory information management system used to manage data, including but not limited to: instrumentation, test articles, standards, and samples.
MPI Archiving System (MArcS) v2.0:	In-house developed application for automated storage and retrieval information for archiveable materials (e.g., lab books, study data, wet tissues, slides, etc.).
Enterprise Reporting System – Table Production System v1.14	In-house developed reporting system used primarily for reporting of Provantis™ data.
eDocs v3.3:	Electronic document management system.
Master Schedule v2.2:	Maintains the master schedule for the company.
MasterControl QAAD v8.0:	A quality management system, consisting of the QAAD and QAADLink applications, used to automate the Quality Assurance process for regulatory compliance.
SAS® v9.1:	The SAS® System is an integrated system of software products that enables a user to perform data entry, retrieval, data management, reporting, graphics, statistical analysis, and applications development.
docuBridge® v3.6/5.1:	Electronic publishing system.
Microsoft® Office Professional 2003/2010:	Suite of integrated productivity tools including word and data processing and communications software.

Additional information is available in the MPI Research, Inc., company document titled “Computer Systems Information.”

Appendix M
Protocol and Amendments

**H-28548: Combined Chronic Toxicity/Oncogenicity Study
2-Year Oral Gavage Study in Rats**

Work Request Number 18405

Service Code 1238

DuPont Report Number – 18405-1238

Protocol

July 8, 2010

TABLE OF CONTENTS

1.	INTRODUCTION	4
1.1.	Study Number	4
1.2.	Study Title.....	4
1.3.	Sponsor	4
1.4.	Sponsor Representative.....	4
1.5.	Objective	4
1.6.	Regulatory Guideline	4
1.7.	Good Laboratory Practice	5
1.8.	Testing Facility	5
1.9.	Computer Systems	5
1.10.	Personnel.....	6
1.11.	Proposed Study Schedule.....	6
1.12.	Quality Assurance.....	7
1.13.	Alteration of Design.....	7
1.14.	Declaration of Intent	7
2.	Test and Control Articles.....	7
2.1.	Description of Test Article.....	7
2.2.	Test Article Preparation	7
2.3.	Test Article Analysis.....	8
2.4.	Analyses.....	8
2.5.	Reserve Sample.....	9
2.6.	Test Article Disposition	9
2.7.	Description of Vehicle	9
3.	Test System.....	9
3.1.	Species	9
3.2.	Strain.....	9
3.3.	Source	10
3.4.	Justification of Test System	10
3.5.	Expected Age.....	10
3.6.	Expected Body Weight	10
3.7.	Number of Animals.....	10
3.8.	Husbandry	11
3.9.	Sentinel Animals.....	12
4.	Study Design.....	14
5.	Test and control Article Administration	14
5.1.	Route of Administration	14
5.2.	Justification for Route of Administration and Dose Selection	14
5.3.	Frequency and Duration of Administration	15
5.4.	Dose Volume	15
5.5.	Test Article Administration	15
6.	Antemortem Study Evaluations.....	15

6.1.	Ophthalmoscopic Examinations	15
6.2.	Cageside Observations.....	15
6.3.	Detailed Clinical Examinations	16
6.4.	Body Weights.....	16
6.5.	Food Consumption.....	16
6.6.	Clinical Pathology.....	16
7.	Euthanasia.....	19
7.1.	Moribundity	19
7.2.	Method of Euthanasia	19
7.3.	Final Disposition.....	19
8.	Postmortem Study Evaluations.....	19
9.	Statistics.....	23
9.1.	Group Pair-Wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's).....	24
9.2.	Log Transformation with Group Pair-wise Comparisons.....	25
9.3.	Rank Transformation with Dunnett's Test	25
9.4.	Survival Analysis.....	25
9.5.	Tumor Analysis.....	25
10.	Study Reports	26
10.1.	Progress/Status Reports	26
10.2.	Final Report	26
11.	Data and Specimen Retention.....	27
12.	Animal Welfare	27
13.	Approval	28
13.1.	Date of Sponsor Approval	28
13.2.	Study Director Approval/Study Initiation.....	28
13.3.	MPI Research Management Approval.....	28

1. INTRODUCTION

1.1. Study Number

DuPont Work Request/Study Code Number: DuPont-18405/1238

DuPont Report Number: 18405-1238

MPI Research Study Number: 125-141

1.2. Study Title

H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

1.3. Sponsor

E.I. du Pont de Nemours and Company
Wilmington, Delaware 19898, U.S.A.

1.4. Sponsor Representative

Susan A. MacKenzie, V.M.D., Ph.D., D.A.B.T.
Senior Research Toxicologist
DuPont Haskell Global Centers for Health and Environmental Sciences
P.O. Box 50
Newark, Delaware 19714 U.S.A.

Telephone: 302-366-6389
Telefax: 302-366-5211
E-mail: Susan.A.MacKenzie@USA.dupont.com

1.5. Objective

The objective of this study is to evaluate the potential chronic toxicity and oncogenicity of H-28548 when administered via oral gavage over the major portion of the life span of the test animals.

1.6. Regulatory Guideline

This protocol meets the United States Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances, Guideline 870.4300, Combined chronic toxicity/carcinogenicity, August 1998. The experimental design and methods are also based on the Organization for Economic Cooperation and Development (OECD) Guideline 453, September 2009, the Japanese Ministry of Agriculture, Forestry and Fisheries Guidelines for Data Requirements for Supporting Registration of Pesticides, No. 12-Nousan-8147, Notification by Director-General dated 24 November, 2000, and the Commission Directive 88/302/EEC B.33 Combined Chronic/Carcinogenicity test, *Methods for the Determination of Toxicity* (1988).

1.7. Good Laboratory Practice

This nonclinical laboratory study will be conducted in accordance with the United States Environmental Protection Agency FIFRA Good Laboratory Practice (GLP) Standards, 40 CFR Part 160, Toxic Substance Control Act Good Laboratory Practice Standards, 40 CFR Part 792, the Organization for Economic Cooperation and Development (OECD) Principles of Good Laboratory Practice ENV/MC/CHEM(98)17, and the Japanese Good Laboratory Practice Standards, 11 Nohsan No. 6283 and as changed in 12 Nohsan No. 8628, and 13 Seisan No. 1660.

1.8. Testing Facility

MPI Research, Inc.
 54943 North Main Street
 Mattawan, MI 49071-9399 U.S.A.

MPI Research is fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International).

1.9. Computer Systems

The following are the proposed computer systems to be used during the conduct of this study. The actual systems used will be documented in the final report.

MPI Research Computer Systems	
Provantis™:	Client-server, Oracle-based system primarily used for toxicology studies.
Niagara Framework® Software System or Siemens Environmental Monitoring System (EMS):	Environmental monitoring, alarming, and reporting application.
Dispense:	Automates the test article control processes.
Microsoft® Windows XP:	Used in conjunction with Empower 2 software
Empower 2:	Empower 2 Chromatographic Data System used to quantitatively determine the amounts of analytes in samples, including test articles in formulation.
MPI Archiving System (MArcS):	In-house developed application for automated storage and retrieval information for archiveable materials (e.g. lab books, study data, wet tissues, slides, etc.).
Enterprise Reporting System – Table Production System (TPS):	In-house developed reporting system used primarily for reporting of Provantis™ data.
Master Schedule:	Maintains the master schedule for the company.

SAS [®] :	The SAS [®] System is an integrated system of software products that enables a user to perform data entry, retrieval, data management, reporting, graphics, statistical analysis, and applications development.
Microsoft [®] Office 2003 Professional:	Bundle of integrated productivity tools including word and data processing and communications software. Contains the utilities Microsoft [®] Access, Excel, InfoPath, Outlook, PowerPoint, Publisher, and Word.
docuBridge [®] :	Electronic publishing system.

1.10. Personnel

1.10.1. Study Director

Lisa Craig, B.S.

Telephone: 269-668-3336 ext. 1367

Telefax: 269-668-4151

E-mail: lisa.craig@mpiresearch.com

1.10.2. Alternate Contact

Chris N. Papagiannis, B.S.

Telephone: 269-668-3336 ext. 1392

Telefax: 269-668-4151

E-mail: chris.papagiannis@mpiresearch.com

1.11. Proposed Study Schedule

Study Initiation Date (EPA and OECD): (Date Study Director signs Study Approval-Initiation Line in the protocol)	Date Study Director signs Study Approval-Initiation Line in this protocol
Experimental Starting Date (OECD): (Date of the first data collection directly from the study)	July 15, 2010
Experimental Start Date (EPA): (Date of first test article exposure)	July 29, 2010
Experimental Termination Date (EPA): (Date of last animal termination)	August 3, 2012
Experimental Completion Date (OECD): (Date of the last data collection directly from the study)	Date Anatomic Pathology Contributor report is signed
Draft Report Mail Date:	To be added by amendment

1.12. Quality Assurance

This study will be subjected to periodic inspections and the data, draft and final reports will be reviewed by the Quality Assurance Department of MPI Research in accordance with MPI Research's Standard Operating Procedures. Study quality assurance inspection records will be made available to the Sponsor Representatives during visits to MPI Research.

1.13. Alteration of Design

Alterations of this protocol may be made as the study progresses. No changes in the protocol will be made without the specific written request or consent of the Sponsor. In the event that the Sponsor authorizes a protocol change verbally, MPI Research will honor such change. However, written authorization will be obtained thereafter. All protocol amendments and justifications will be documented, signed, and dated by the Study Director and Sponsor. The protocol and all amendments will be issued to the Sponsor as well as at MPI Research.

1.14. Declaration of Intent

This study may be submitted to an Organization for Economic Cooperation and Development (OECD) member country, the United States Environmental Protection Agency (EPA), and/or other country regulatory bodies.

2. TEST AND CONTROL ARTICLES

2.1. Description of Test Article

2.1.1. Identity

HFPO Dimer Acid Ammonium Salt

Haskell number: 28548

R&D Lot Number: E109540-44A

A description, lot number, storage conditions, expiration date, safe handling procedures, physical properties, as well as other relevant information will be documented in the study data.

2.1.2. Test Article Properties

The Sponsor will provide a certificate of analysis (COA) documentation on the purity, composition, stability, and other pertinent information, unless otherwise noted.

2.2. Test Article Preparation

The bulk test article will be stored at room temperature. The test article formulations will be adjusted for a purity of 84%. The test article will be mixed with deionized water to achieve the desired dose volumes. The vehicle and method of preparation will be determined based upon physical characteristics of the test article and size of batches required. Fresh formulations will be prepared for each concentration weekly and stored at room temperature when not in use.

2.3. Test Article Analysis

Test article formulations prepared for the study will be evaluated for homogeneity and concentration. Room temperature stability (at least 14 days) which covers the concentration range to be used in this study has been established in MPI Research Study Number 125-128. No further stability analysis is necessary.

Appropriate samples (see table below) will be taken while the preparations are stirring. Homogeneity will be evaluated again if the batch size changes by more than 50% during the study or if a new concentration is outside of the range of concentrations previously evaluated. Following acceptance of the analytical results (signing of the final report) by the Study Director, or at the Study Director's discretion, backup samples will be discarded.

Analytical Sample Collection Table

Sample Type	Concentrations to Sample	Stratum	Number of Samples per Concentration			Sample Volume (mL)	Intervals
			Collected	Analyzed	Back up		
Homogeneity Analyses ^a	All (except control)	Top	6	2	4	1	Week 1
		Middle	6	2	4	1	
		Bottom	6	2	4	1	
Concentration Analyses ^a	All (including control)	Middle	6	2	4	1	Weeks 1-4, every 3 months thereafter

^a: The samples will be stored frozen at approximately -20 °C pending analyses or final disposition.

2.4. Analyses

All analytical work will be conducted by MPI Research, Inc., State College, PA using an analytical method developed by MPI Research and validated under MPI Research Study Number 125-128. The work performed in conjunction with this study will be conducted in compliance with GLPs and subject to review by the Quality Assurance Unit (QAU) of that laboratory. The findings of their QAU will be submitted to the Principal Investigator and the Principal Investigator's Management as well as to the MPI Research Study Director and MPI Research Management. A final report, including a Quality Assurance Statement, will be prepared and submitted to MPI Research for inclusion as an appendix in the main study final report. Samples will be shipped on dry ice on Monday through Wednesday for next day delivery. The primary contact will be notified prior to each shipment.

Principal Investigator (Formulation Analyses)	Primary Contact for Sample Shipment
Sharon Lupo 3058 Research Drive State College, PA 16801 Telephone: 814-272-1039	Attn: Sample Control 3048 Research Drive State College, PA 16801 Telephone: 814-272-1039

Telefax: 814-231-1580 E-mail: Sharon.lupo@mpiresearch.com	Telefax: 814-231-1580 E-mail: SC1SampleReceiving@mpiresearch.com
--	---

2.5. Reserve Sample

A reserve sample from each batch of test article used in this study will be collected and stored at MPI Research in a secure area with the appropriate environmental controls. If multiple studies are conducted with the same test article, a common reserve sample may be taken and labeled appropriately.

2.6. Test Article Disposition

Any remaining test article will be returned to the Sponsor after completion of the study. The test article will be shipped to the following address:

Laura N. Smith
E.I. du Pont de Nemours and Company
Stine Haskell Research Center
Building S120/103
1090 Elkton Road
Newark, DE 19714
Telephone: 302-366-5542

Ms. Smith will be notified prior to shipment.

2.7. Description of Vehicle

2.7.1. Identity

Deionized water

A description, lot number, storage conditions, expiration date, safe handling procedures, physical properties, as well as other relevant information will be documented in the study data.

2.7.2. Vehicle/Control Article Properties

The vehicle used will be from deionized tap water at the Testing Facility.

3. TEST SYSTEM

3.1. Species

Rat

3.2. Strain

CD[®] [CrI:CD(SD)]

3.3. Source

Charles River Laboratories

3.4. Justification of Test System

The current state of scientific knowledge and the applicable guidelines cited previously in this protocol do not provide acceptable alternatives, *in vitro* or otherwise, to the use of live animals to accomplish the purpose of this study. “The development of knowledge necessary for the improvement of the health and well-being of humans as well as other animals requires *in vivo* experimentation with a wide variety of animal species.”¹ “Whole animals are essential in research and testing because they best reflect the dynamic interactions between the various cells, tissues, and organs comprising the human body.”²

The rat is a frequently used model for evaluating the toxicity of various classes of chemicals and for which there is a large historical database.

3.5. Expected Age

The test animals will be approximately 4-5 weeks of age at arrival. All animals placed on study will be less than 8 weeks of age at the start of dosing.

3.6. Expected Body Weight

The males will weigh approximately 100 to 125 g and the females will weigh approximately 76 to 100 g at arrival, as measured within 3 days of arrival. The actual range may vary but will be documented in the data.

3.7. Number of Animals

3.7.1. Number Ordered

Males: 400
Females: 400

3.7.2. Number on Study (includes 25 sentinel animals per sex)

Males: 345
Females: 345

Females will be nulliparous and non-pregnant.

3.7.3. Justification for Number on Study

This study was designed to use the fewest number of animals possible, consistent with the objective of the study, the scientific needs of the Sponsor, contemporary scientific standards, and in consideration of applicable regulatory requirements cited previously in this protocol.

¹ “Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training”, Federal Register, 1985 May 20; 50(97).

² “Position Statement on the Use of Animals in Research”, 1993 Feb 26; NIH Guide 22(8).

This study is designed to use the smallest number of animals possible that will allow sufficient group sizes for meaningful statistical analysis of data.

3.7.4. Selection for Study

All animals placed on study will have body weights that fall within $\pm 20\%$ of the mean body weight for each sex. If not enough animals fall within this weight range to satisfy the number of animals required to go on study, the Study Director will be notified to ascertain the appropriate action to be taken.

Animals considered suitable for study will be weighed prior to treatment. After the appropriate number of animals with the highest and lowest body weights has been excluded, the remaining required number of animals on study will be randomized, by sex, into treatment groups using a standard, by weight, measured value randomization procedure.

3.7.5. Method of Identification

Each animal will be assigned an animal number to be used in Provantis[™] and will be implanted with a microchip bearing a unique identification number. The individual animal number, implant number, and the MPI Research study number will comprise a unique identification for each animal. The animal cage will be identified by the study number, animal number, group number, and sex.

3.8. Husbandry

3.8.1. Acclimation

All animals will be permitted an acclimation period of approximately 2 weeks. During this acclimation period, all animals will be observed daily for any clinical signs of disease and all animals will be given a detailed clinical examination prior to selection for study. All animals with any evidence of disease or physical abnormalities will not be selected for study. The week prior to dose initiation, animals will be administered a sham dose of tap water on at least 2 occasions in the same manner and at the same volume intended for use during the study period.

3.8.2. Housing

The animals will be pair-housed (same sex) in solid-bottom cages (polyboxes). In order to foster the rat's natural chewing instinct and keep their teeth at a healthy length, approved chew toys (e.g. Nylabone) will be offered.

3.8.3. Environmental Conditions

Fluorescent lighting will be provided via an automatic timer for approximately 12 hours per day. On occasion, the dark cycle may be interrupted intermittently due to study-related activities. Temperature and humidity will be monitored and recorded daily and maintained to the maximum extent possible between 64 to 79° F and 30 to 70%, respectively.

3.8.4. Diet and Drinking Water

3.8.4.1. Basal Diet

The basal diet will be block Lab Diet® Certified Rodent Diet #5002, PMI Nutrition International, Inc. This diet will be available *ad libitum* unless designated otherwise. Each lot number used will be identified in the study records.

3.8.4.2. Basal Diet Contaminants

The Study Director is not aware of any potential contaminants likely to be present in the certified diet that would interfere with the results of this study. Therefore, no analyses other than those routinely performed by the feed supplier will be conducted.

3.8.4.3. Water

Tap water will be supplied *ad libitum* via an automatic water system unless otherwise indicated.

3.8.4.4. Water Contaminants

The drinking water used will be monitored for specified contaminants at periodic intervals according to MPI Research Standard Operating Procedures. The Study Director is not aware of any potential contaminants likely to be present in the water that would interfere with the results of this study. Therefore, no analyses other than those mentioned in this protocol will be conducted.

3.9. Sentinel Animals

A health screen will be conducted pretest and at 6, 12, 18, and 24 months on 3-5 males and 3-5 females (depending on survival) using sentinel animals selected with a computerized randomization and euthanized via carbon dioxide inhalation for this purpose. If insufficient animals are available due to survival, fewer animals may be submitted for evaluation (Study Director consulted) and this will be noted in the final report. Approximately 1-2 mL of blood will be collected via the vena cava and serum obtained. Blood samples will be processed to serum and placed into 2 aliquots of approximate equal volume. Serum samples will be stored at approximately -20°C. A gross necropsy will be performed at the time of blood collection. Gross lesions will be recorded. No tissues will be saved. Any sentinel animal that is found dead or euthanized *in extremis* will receive a gross necropsy and gross lesions will be saved for possible histopathologic evaluation.

The serum will be evaluated as indicated below:

3.9.1. Pretest and at months 12 and 24

- Pneumonia Virus
- Reovirus Type 3
- Theiler's Encephalomyelitis Virus (GD-7)
- Lymphocytic Choriomeningitis Virus

- Sendai Virus
- Mycoplasma Pulmonis
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus

3.9.2. At months 6 and 18

- Sendai Virus
- Kilham Rat Virus
- Rat Coronavirus/Sialodacryoadenitis Virus
- Toolan's H-1 Virus
- Rat Parvovirus
- Mycoplasma Pulmonis

Initial testing will be performed at MPI Research. For positive or inconclusive results, confirmation testing will be performed by BioReliance. Samples will be sent at ambient temperature to the following address, if necessary.

Principal Investigator: Dr. Arlene Leon
BioReliance Corporation

9900 Blackwell Road
Rockville, MD 20850

Telephone: 301-610-2641
Telefax: 301-610-2587

Any actions based on the results of the health screen will be determined after consultation with the Sponsor. Testing will not be conducted in accordance with GLPs. This will be included as a GLP exception in the final report. Results of these analyses will be maintained in the study file.

4. STUDY DESIGN

G R O U P	Dose Level (mg/kg/day)	Number of Animals									
		Initial		Clinical Pathology ^a		12-Month Interim Necropsy ^{a, b}		Terminal Necropsy		Microscopic Pathology ^c	
		M	F	M	F	M	F	M	F	M	F
1	0	80	80	10	10	10	10	70	70	80	80
2	0.1	80	-	10	-	10	-	70	-	AR	-
3	1	80	80	10	10	10	10	70	70	AR	AR
4	50	80	80	10	10	10	10	70	70	80	AR
5	500	-	80	-	10	-	10	-	70	-	80
89*	-	25	25	-	-	-	-	-	-	-	-

a: Hematology, and clinical chemistry will be performed on 10 animals/sex/group at 3 months. Hematology, coagulation, clinical chemistry, and urinalysis evaluations will be conducted on 10 animals/sex/group at 6 and 12 months. Differential blood smear will be prepared on all animals designated for necropsy at 12 months, all survivors at 12, 18, and 24 months (termination), and all animals euthanized in extremis.

b: An interim necropsy will be conducted at 12 months on 10 animals/sex/group.

c: Animals from both the 12 month interim and terminal necropsies, and other animals as required..

AR = As Required: 1) Target tissues identified by high dose group evaluations, 2) Tissues in all animals found dead or euthanized in a moribund condition, and 3) gross lesions.

**Sentinel animals*

5. TEST AND CONTROL ARTICLE ADMINISTRATION

5.1. Route of Administration

The test and control articles will be administered by gavage.

5.2. Justification for Route of Administration and Dose Selection

The oral gavage route was selected as the most efficient way to administer an accurate dose.

In a previous study (DuPont-17751-1026), Crl:CD(SD) rats (10/sex/dose) were dosed with the test substance by oral gavage for at least 90 days at daily doses of 0, 0.1, 10, or 100 mg/kg/day for males and 0, 10, 100, or 1000 mg/kg/day for females. In the 1000 mg/kg/day group, three females died prior to scheduled sacrifice and others displayed clinical signs. No other test substance-related effects were observed in surviving animals in all groups on body weight or nutritional parameters, clinical or ophthalmological observations, or neurobehavioral parameters.

Test substance-related findings included regenerative anemia (males: 100 mg/kg/day; females: 1000 mg/kg/day), clinical chemistry effects consistent with PPAR α activation (males: ≥ 10 mg/kg/day; females: 100-1000 mg/kg/day), and increased liver weights and associated hepatocellular hypertrophy (males: ≥ 10 mg/kg/day; females: 1000 mg/kg/day). Similar liver effects were observed at ≥ 3 mg/kg/day in males and 300 mg/kg/day in females in a rat 28-day gavage study (DuPont-24447). Increased kidney weights were observed in males and females at ≥ 10 mg/kg/day. In females, renal papillary necrosis and/or renal

tubular necrosis were observed in the two females found dead prior to scheduled sacrifice and in one female that survived to the scheduled sacrifice. Clinical and anatomic pathology parameters were fully or partially (male hematology effects; liver weights) reversible after an approximate 4-week recovery period.

Based on the results of the 90-day and 28-day studies, doses selected for this study were 0, 0.1, 1, and 50 mg/kg/day in males and 1, 50, and 500 mg/kg/day in females. The high dose is expected to produce effects on clinical chemistry and liver weight and microscopic pathology in males and females, without producing excessive liver toxicity. The middle dose may produce liver and clinical chemistry in either sex but could be a no-observed-adverse-effect level (NOAEL). The low dose is expected to be a NOAEL in both males and females.

5.3. Frequency and Duration of Administration

The test and control articles will be administered once per day, at approximately the same time of day (i.e., if the Day 1 dose occurs in the am, then subsequent doses should be delivered in the am for the study duration), for at least 104 weeks. The animals will be dosed up to the day prior to scheduled necropsy.

5.4. Dose Volume

10 mL/kg/dose

5.5. Test Article Administration

For administration, the test and control articles will be dosed via oral gavage in accordance with SOP TMA-1. The control animals will receive the control article at the same volume as the test article. Individual doses will be based on the most recent body weights.

6. ANTEMORTEM STUDY EVALUATIONS

6.1. Ophthalmoscopic Examinations

All animals in all groups will be examined prior to exposure and all surviving animals prior to the scheduled necropsy (interim and terminal) in accordance with SOP TOX-61. The ophthalmological examinations will be conducted by a veterinary ophthalmologist.

6.2. Cageside Observations

All animals will be observed at least twice a day for morbidity, mortality, injury, and availability of food and water in accordance with SOP ACU-65. The afternoon cageside observation will be conducted at the same approximate time of day (± 2 hours). Beginning on Week 53, a third mortality check in the evening will also be conducted. Any animals in poor health will be identified for further monitoring and possible euthanasia.

Any abnormal findings noted in the morning cageside observation will be recorded by exception (i.e., 'no abnormalities detected' will not be captured on a daily basis for every animal).

6.3. Detailed Clinical Examinations

A detailed clinical examination of each animal will be performed once during each study week in accordance with SOP TOX-2. Observations will include, but will not be limited to, evaluation of the skin, fur, eyes, ears, nose, oral cavity, thorax, abdomen, external genitalia, limbs and feet, respiratory and circulatory effects, autonomic effects such as salivation, and nervous system effects including tremors, convulsions, reactivity to handling, bizarre behavior, and palpation of tissue masses in accordance with SOP TOX-3.

6.4. Body Weights

Body weights will be measured and recorded within 3 days of arrival, at least once prior to randomization, weekly during the first 13 weeks starting on Day 1 (prior to dosing), and every other week thereafter in accordance with SOP TOX-4. The individual and mean group mean body weights gain will be calculated and reported weekly (starting on Week -1), for the first quarter (Weeks 1-13), the first year (Weeks 1-52), and the entire study (Weeks 1-104).

6.5. Food Consumption

Food consumption will be measured and recorded pretest (Week -1), weekly during the first 13 weeks, and for 2 weeks intervals starting at Week 14 (i.e., food consumption will represent a 14 day interval) in accordance with SOP TOX-5. Food consumption will be measured for the cage and divided by the number of surviving animals. The individual and mean group mean food consumption and food efficiency will be calculated and reported weekly (starting on Week -1), for the first quarter (Weeks 1-13), the first year (Weeks 1-52), and the entire study (Weeks 1-104).

6.6. Clinical Pathology

The animals will have free access to drinking water but will be fasted overnight (no more than 16 hours) prior to sample collection. Blood samples (approximately 3 mL) taken at non-terminal intervals will be taken via the sublingual vein. Blood samples (3-5 mL) taken at necropsy will be taken via the vena cava. Blood samples (0.5 mL) for blood smears taken from animals not scheduled for full clinical pathology evaluation or euthanized *in extremis*, where possible, will be taken via the sublingual vein. Where possible, the animals designated for clinical pathology evaluations at 3 and 6 months will be the same animals evaluated at 12 months.

The order of bleeding and analysis will be alternating (one animal from each dose group, then repeating) to reduce handling and time biases. If samples need to be recollected for hematology, coagulation, or urinalysis for sample quality purposes (e.g., clotted sample), animals do not need to be fasted.

The following clinical pathology tests will be conducted.

6.6.1. Hematology

6.6.1.1. Number of Animals

10/sex/group at 3, 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.1.2. Collection Intervals

3, 6, and 12 months

6.6.1.3. Parameters Evaluated

- leukocyte count (total and absolute differential)
- erythrocyte count
- hemoglobin
- hematocrit
- mean corpuscular hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration (calculated)
- absolute reticulocytes
- platelet count
- blood cell morphology

6.6.2. Coagulation

6.6.2.1. Number of Animals

10/sex/group at 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.2.2. Collection Intervals

6 and 12 months

6.6.2.3. Parameters Evaluated

- prothrombin time
- activated partial thromboplastin time

6.6.3. Clinical Chemistry

6.6.3.1. Number of Animals

10/sex/group at 3, 6, and 12 months (Animals designated for chronic toxicity evaluation)

6.6.3.2. Collection Intervals

3, 6, and 12 months

6.6.3.3. Parameters Evaluated

- alanine aminotransferase
- alkaline phosphatase
- sorbitol dehydrogenase
- total protein

- albumin
- globulin and A/G (albumin/globulin) ratio (calculated)
- urea nitrogen
- creatinine
- total cholesterol
- triglycerides
- total bilirubin (with direct bilirubin if total bilirubin exceeds 1 mg/dl)
- aspartate aminotransferase
- total bile acids
- glucose
- calcium
- phosphorus
- electrolytes (sodium, potassium, and chloride
- gamma glutamyl transferase

6.6.4. Urinalysis

Animals will be placed in stainless steel metabolism cages for at least 12 hours to collect urine.

6.6.4.1. Number of Animals

10/sex/group at 6 and 12 months (Animals designated for chronic toxicity evaluation)

6.6.4.2. Collection Intervals

6 and 12 months

6.6.4.3. Parameters Evaluated

- volume
- specific gravity
- pH
- color and appearance
- protein
- glucose
- bilirubin
- ketones
- blood
- urobilinogen
- microscopy of centrifuged sediment

6.6.5. Peripheral Blood Smears

6.6.5.1. Number of Animals

All surviving animals (animals designated for carcinogenicity evaluation) and just prior to necropsy for animals euthanized *in extremis*

6.6.5.2. Collection Intervals

12 and 18 months and prior to termination (24 months)

Peripheral blood smears will be prepared and held for possible future analysis from all surviving animals at 12, 18, and 24 months (study termination). The total and differential leukocyte count will be made on those animals in the control and highest dose group (Groups 1 and 4 or 5) at termination. If these data, or data from the pathology examination, indicate a need, then the blood smears from the other dose groups and/or earlier time point will also be examined. If clinical observations suggest a deterioration of health of the animals during the study, a differential blood count of the affected animals will be performed.

7. EUTHANASIA

7.1. Moribundity

Any moribund animals, as defined by a Testing Facility Standard Operating Procedure (ACU-47), will be euthanized for humane reasons and to prevent the loss of tissues through autolysis. All animals euthanized *in extremis* or found dead will be subjected to a routine necropsy. Where practical, a full set of tissues as listed in the Postmortem Study Evaluations portion of this protocol will be collected and preserved in the appropriate fixative.

7.2. Method of Euthanasia

Euthanasia will be by carbon dioxide inhalation followed by a MPI Research SOP (NEC-12) approved method to ensure death, e.g. exsanguination.

7.3. Final Disposition

All surviving animals placed on study will be euthanized at their scheduled necropsy or, if necessary, euthanized *in extremis*. Extra animals obtained for this study, but not placed on study, will be transferred to either an MPI Research stock or training colony, or euthanized and discarded. The final disposition of each animal will be documented in the study records.

8. POSTMORTEM STUDY EVALUATIONS

Complete necropsy examinations will be performed under procedures approved by a veterinary pathologist on all animals dying spontaneously, euthanized *in extremis*, or euthanized at scheduled necropsies in accordance with SOP NEC-42. Examinations will be performed 7 days a week. Animals that are found dead after regular working hours will be refrigerated overnight and necropsies performed at the start of the next working day. At the appropriate intervals (after 12 and 24 months), all appropriate animals will be euthanized and examined.

The animals will be examined carefully for external abnormalities including palpable masses. The skin will be reflected from a ventral midline incision, and any subcutaneous masses will be identified and correlated with antemortem findings. The abdominal, thoracic, and cranial cavities will be examined for abnormalities and the organs removed, examined, and, where

required, placed in fixative. The pituitary will be fixed *in situ*. The eyes and testes will be fixed using a modified Davidson's fixative³. All other tissues will be fixed in neutral buffered formalin. Formalin will be infused into the lung via the trachea and into the urinary bladder.

Body weight and the organ weights identified in the following table will be recorded for all animals at scheduled necropsies and appropriate organ weight ratios will be calculated (relative to body and brain weights). Paired organs will be weighed together. A combined weight of the thyroid gland with the bilateral parathyroid post fixation will be obtained. Organs will not be weighed for animals dying spontaneously or euthanized *in extremis*.

Microscopic examination of fixed hematoxylin and eosin-stained paraffin sections will be performed on sections of tissues and from the groups identified in the following table and all animals dying spontaneously or euthanized *in extremis*.

Organs or Tissues to be Weighed, Preserved, and Microscopically Examined

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) ^a	
			1, 4/5	2-3/4
Adrenal gland	X	X	X	
Aorta		X	X	
Bone with bone marrow, femur		X	X	
Bone with bone marrow, sternum		X	X	
Bone marrow smear ^b		X		
Brain (cerebrum, midbrain, cerebellum, medulla/pons)	X	X	X	
Coagulating gland		X	X	
Epididymis	X	X	X	
Esophagus		X	X	
Eye (with retina and optic nerve)		X	X	
GALT ^c		X	X	
Harderian gland		X	X	

³ Latendresse JR, Warbritton AR, Jonassen H, Creasy DM. Fixation of testes and eyes using a modified Davidson's fluid: comparison with Bouin's fluid and conventional Davidson's fluid. Toxicol Pathol. 2002 Jul-Aug;30(4):524-33.

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) ^a	
			1, 4/5	2-3/4
Heart	X	X	X	
Joint, tibiofemoral		X	X	
Kidney	X	X	X	
Lacrimal gland, exorbital		X	X	
Large intestine, cecum		X	X	
Large intestine, colon		X	X	
Large intestine, rectum		X	X	
Larynx		X	X	
Liver	X	X	X	
Lung with bronchi		X	X	
Lymph node, mandibular		X	X	
Lymph node, mesenteric		X	X	
Mammary gland (process females only)		X	X	
Nerve, sciatic		X	X	
Nose (4 sections)		X	X	
Ovary with oviduct	X	X	X	
Pancreas		X	X	
Pharynx		X	X	
Pituitary		X	X	
Prostate		X	X	
Salivary gland, mandibular		X	X	
Salivary gland, parotid		X	X	
Salivary gland, sublingual		X	X	
Seminal vesicles		X	X	
Skeletal muscle, biceps femoris		X	X	
Skin		X	X	
Small intestine, duodenum		X	X	
Small intestine, ileum		X	X	

Tissue	Organ Weight Taken	Collected and Preserved	Microscopic Examination (Groups) ^a	
			1, 4/5	2-3/4
Small intestine, jejunum		X	X	
Spinal cord, cervical		X	X	
Spinal cord, lumbar		X	X	
Spinal cord, thoracic		X	X	
Spleen	X	X	X	
Stomach, glandular		X	X	
Stomach, nonglandular		X	X	
Target Organs ^d		X	X	X
Testis	X	X	X	
Thymus		X	X	
Thyroid gland (with parathyroid) ^e	X	X	X	
Tongue		X	X	
Trachea		X	X	
Ureters		X	X	
Urinary bladder		X	X	
Uterus with cervix	X	X	X	
Vagina		X	X	
Gross lesions		X	X	X
Tissue masses with regional lymph node ^f		X	X	X

^a Microscopic examination will be conducted in controls and in Group 4 males and Group 5 females, the respective high dose for each sex.

^b Bone marrow smears will be prepared only for animals necropsied at scheduled intervals. Evaluation will be performed at the discretion of the Study Director and/or Sponsor (additional cost).

^c Gut associated lymphoid tissue

^d Target organs (and target organ gross lesions) will be designated by the Study Director, Pathologist and/or Sponsor based on experimental findings (additional cost).

^e Parathyroids cannot always be identified macroscopically. They will be examined if in the plane of section and in all cases where they are noted as grossly enlarged.

^f A regional lymph node drains the region where a tissue mass is located.

The presence of test article-related lesions in animals from the high dose group will require microscopic examination of the affected target tissue(s) in all animals from the lower dose groups. If mortality in the high dose groups is sufficiently high to preclude assessment of a potential toxic response, all protocol-required tissues from all animals in the next lower dose group will be examined after consultation with the Sponsor (additional cost).

The pathologist may use special stains and techniques as needed to aid in the diagnosis of specific lesions. If after routine sectioning, a tissue is missed, the block will be resectioned once or the tissue re-embedded for resectioning. If the tissue is still missing, the block will not be resectioned unless the missing tissue is determined to be a target organ. In this case, the tissue will be resectioned until located or until it is determined that it is not present in the block or in wet tissue. All missing tissues will be identified in the pathology portion of the final report. Tissues that are unintentionally sectioned or present in the plane with a required tissue, though not required by protocol, will be examined and documented, if abnormal.

A pathologist other than the study pathologist will perform a formal peer review of the histopathologic findings. This review will consist of an examination of all tissues determined to be target organs by the study pathologist, all neoplasms diagnosed in the study and all tissues from 10% of the animals selected randomly from control and high dose groups. Other selected tissues may be examined at the discretion of the reviewing pathologist. A signed statement by the reviewing pathologist will appear in the final report.

9. STATISTICS

The following is the proposed analysis plan to be used when data assumptions are met. If there are deviations to this plan due to violations of assumptions or if any other techniques are used (Sponsor consulted), they will be documented in the final report.

Table of Statistical Comparisons

Control Group	Treatment Groups
1	2, 3, 4, 5

The above table defines the set(s) of comparisons to be used in the statistical analyses described below. If more than one set of comparisons is required, all analyses will be conducted separately on each set unless stated otherwise. Data for each sex within a set will also be analyzed separately.

The raw data will be tabulated within each time interval, and the mean and standard deviation will be presented for each endpoint by sex and group. For each endpoint, treatment groups will be compared to the control group using the analysis outlined below. Data for some endpoints, as indicated, will be transformed by either a log or rank transformation prior to conducting the specified analysis.

Endpoints	Type of Analysis
Body Weight Body Weight Gain Food Consumption Hematology (except Leukocyte Counts) Coagulation Clinical Chemistry Organ Weights Absolute Weights Relative to Body and Brain Weight	Group Pair-wise Comparisons
Leukocyte Counts Total Leukocyte Counts Differential Leukocyte Counts	Log Transformation Group Pair-wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)
Urinalysis Urine Volume Specific Gravity pH	Rank Transformation with Dunnett's Test
Mortality Data	Survival Analysis
Tumor Data	Tumor Analysis
Non-Tumor Microscopic Pathology Data	To be determined if required

9.1. Group Pair-Wise Comparisons (Levene's/ANOVA-Dunnett's/Welch's)

If sample sizes for all groups are 3 or greater, Levene's test⁴ will be used to assess homogeneity of group variances for each specified endpoint (see table above) and for all collection intervals. If Levene's test is not significant ($p \geq 0.01$), a pooled estimate of the variance (Mean Square Error or MSE) will be computed from a one-way analysis of variance (ANOVA) and utilized by a Dunnett's⁵ comparison of each treatment group with the control group. If Levene's test is significant ($p < 0.01$), comparisons with the control group will be made using Welch's t-test⁶ with a Bonferroni correction.

In the case that sample size is less than 3 for at least one treatment group, Levene's method cannot be implemented. Groups with sample sizes less than 3 will be excluded from the analysis and control-treatment pair-wise comparisons that satisfy the sample size assumption ($n \geq 3$) will be conducted using Welch's t-test with a Bonferroni correction.

⁴ Milliken GA, Johnson DE. Analysis of messy data. London: Chapman and Hall: 1992.

⁵ Dunnett, CW. A multiple comparison procedure for comparing several treatments with a control. J Am Stat Assoc 1955;50:1096-1121.

⁶ Welch BL. The significance of difference between two means when the population variances are unequal. Biometrika 1937;29:350-362.

If there are only 2 groups involved, the above methodology applies and the Dunnett's test reduces to a Student's t-test⁷.

Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

9.2. Log Transformation with Group Pair-wise Comparisons

Historical data indicates that leukocyte counts (total and differential) are not normally distributed; therefore, a log transformation will be performed on these data. The transformed data will then be analyzed as described in the Group Pair-wise Comparisons section.

9.3. Rank Transformation with Dunnett's Test

Historical data indicate that this endpoint has unpredictable distribution characteristics, thus analysis would be enhanced by use of a non-parametric test. For each specified endpoint (see table above) and for each collection interval, a rank transformation will be performed. The transformed data will then be analyzed using Dunnett's test, to compare each treatment group with the control group.

If sample size for the control group is 2 or greater, Dunnett's test will be used to compare each treatment group having a non-zero sample size with the control group.

If there are only 2 groups involved, the above methodology applies and the Dunnett's test reduces to a Student's t-test⁷. Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests unless indicated otherwise.

9.4. Survival Analysis

Intercurrent mortality data will be analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups will be conducted using a log-rank test⁸. If this overall test is significant ($p < 0.05$) and there are more than two groups, then a follow up analysis will be done where each treatment group will be compared to the control group using a log-rank test.

Results of all pair-wise comparisons will be reported at the 0.05 and 0.01 significance levels. All endpoints will be analyzed using two-tailed tests.

9.5. Tumor Analysis

Tumor incidence data will be analyzed using both survival adjusted and unadjusted tests. The unadjusted tests will be based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage trend test⁹ will be calculated and Fisher's exact test¹⁰

⁷ Steel RGD, Torrie JH. Principles and Procedures of Statistics. A biometrical approach. New York: McGraw-Hill; 1980.

⁸ Allison PD. Survival analysis using the SAS system: A Practical Guide. Cary (NC). SAS Institute Inc.; 1995.

⁹ Agresti A. Categorical data analysis. 2nd ed. New York: John Wiley and Sons; 2002.

will be used to compare each treatment group with the control group. The survival adjusted test will be conducted according to the prevalence/mortality methods described by Peto et al.¹¹. Evaluation criteria (p-values of significance) will be applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%)¹². The evaluation criteria are given in the following table.

Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Electronic data will be provided for this study with the final report. The format of the data sets will be prepared following the guidelines of the United States Environmental Protection Agency (EPA).

10. STUDY REPORTS

10.1. Progress/Status Reports

Regular progress reports will be submitted to the Sponsor weekly for the first 5 weeks and biweekly reports through the first quarter (Week 13). Thereafter, progress reports will be sent approximately once per month.

10.2. Final Report

After completion of the study, a comprehensive draft report containing the results of all tests, analyses, observations and measurements required by this protocol, and an interpretative summary of the study results will be submitted to the Sponsor. The report will include all items required by the applicable regulatory agency. After receipt of any Sponsor comments, 1 copy (unbound) of the final report will be issued. An electronic copy (PDF) will be provided with the final report. This electronic copy will be searchable, hyperlinked (including headings, tables, figures, references, and all tables of contents), and bookmarked. One electronic copy will be in Microsoft Word, where possible. The electronic copies can be sent on CDs.

Six months after issuance of the draft report, if no requested revisions or instructions to finalize have been communicated by the Sponsor, the draft report will be issued as a final

¹⁰ Zar JH. Biostatistical Analysis. 4th ed. New Jersey: Prentice Hall; 1999.

¹¹ Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Pete J, Richards S, Wahrendorf J. Guidelines for simple, sensitive significance tests for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal. Annex to Supplement 2. p. 311-426. International Agency for Research on Cancer, Lyon; 1980.

¹² Haseman JK. A reexamination of false-positive rates for carcinogenesis studies. Fund Appl Toxicol 1983;3:334-339.

report, signed by the Study Director, and submitted to the Sponsor. Any modifications or changes to the draft report requested 6 months after issuance of the draft will be performed at additional cost to the Sponsor.

11. DATA AND SPECIMEN RETENTION

All raw data, documentation, records, protocol, specimens, samples and the final report generated as a result of this study will be retained at MPI Research or an MPI Research contracted archive facility for a period of 1 year following the issuance of the draft report. The Sponsor will be contacted annually by MPI Research Archive staff regarding the retained material and will be responsible for the incurred costs for the return, disposal, or continued storage of any study generated material retained after that time.

12. ANIMAL WELFARE

MPI Research is committed to complying with all applicable regulations governing the care and use of laboratory animals. Animal welfare for this study will be in compliance with the U.S. Department of Agriculture's (USDA) Animal Welfare Act (9 CFR Parts 1, 2 and 3). The Guide for the Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Academy Press, Washington, D.C., 1996, will be followed. This facility maintains an Animal Welfare Assurance statement with National Institutes of Health, Office of Laboratory Animal Welfare.

To ensure compliance:

- A. This protocol will be reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) before animal receipt or transfer.
- B. The Sponsor, by his or her approval, attests that the activities specified in this protocol do not unnecessarily duplicate any previous experiment.
- C. The Study Director has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animal and has signified that (select one):

- ☒ i.) The relevant supervisory government agency currently gives no alternatives.
- ☐ ii.) The following literature searches have been performed to determine whether an alternative species could be used or another procedure to reduce any pain or distress was available and none was found.

Date: November 17, 2009

Literature Search Reference Number: 0001

Interval Searched: All years to Present

Search terms: general alternative testing methods; alternative testing methods, toxicology; general toxicology testing method alternatives

Databases searched: toxnet.nlm.nih.gov;pubmed.gov;medscape.com;caat.jhsph.edu

- iii.) This study does not require any procedures that may cause more than slight or momentary pain or distress to the animal. Note, unknown test articles are presumed to have the potential to cause more than slight pain or distress.

13. APPROVAL

13.1. Date of Sponsor Approval

12-Jul-2010
Date

13.2. Study Director Approval/Study Initiation

Lisa Craig
Lisa Craig, B.S.
Study Director

12-Jul-2010
Date

13.3. MPI Research Management Approval

David G. Serota
David G. Serota, Ph.D., D.A.B.T.
Senior Vice President, Drug Safety Evaluation

7/12/10
Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 1

Page 1 of 1

Item	Revision or Clarification
------	---------------------------

1. **Section 6.4, Body Weights**

Change:

Body weights will be measured and recorded within 3 days of arrival, at least once prior to randomization, weekly during the first **14** weeks starting on Day 1 (prior to dosing), and every other week thereafter in accordance with SOP TOX-4.

Item	Justification
------	---------------

- | | |
|----|--|
| 1. | Updated to take body weights in week 14 due to food consumption measured in week 14. |
|----|--|

Approved by:

24-Sep-2010

Date of Sponsor
Approval

Lisa Craig
Lisa Craig, B.S.
Study Director

24-Sep-2010
Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 2

Page 1 of 1

Item	Revision or Clarification
------	---------------------------

1. **Section 9. Statistics**

Add:

Food efficiency will be statistically analyzed using Rank Transformation with Dunnett's Test.

Effective Date: November 10, 2010

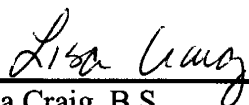
Item	Justification
------	---------------

1. The method of statistically analyzing food efficiency was added.

Approved by:

12-Nov-2010

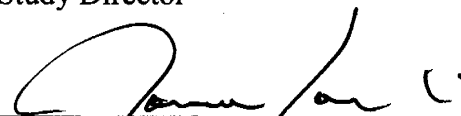
Date of Sponsor
Approval



Lisa Craig, B.S.
Study Director

12-Nov-2010

Date



James G. Laveglia, Ph.D.
Executive Vice President Drug Safety
Evaluation

11/18/10

Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 3

Page 1 of 2

Item	Revision or Clarification
1.	Section 2.3.4. Analysis <u>Change to:</u> Principal Investigator (Formulation Analysis): Jennifer Boughton, M.S. Telephone: 814-272-1039 ext. 4248 Telefax: 814-231-1580 E-mail: jennifer.boughton@mpiresearch.com

Effective Date: November 17, 2010

Item	Justification
1.	Principal Investigator updated due to change in personnel.

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 3

Page 2 of 2

Approved by:

17-Nov-2010

Date of Sponsor
Approval

Lisa Craig

Lisa Craig, B.S.
Study Director

17-Nov-2010

Date

James G. Laveglia

James G. Laveglia, Ph.D.
Executive Vice President Drug Safety Evaluation

11/19/10

Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 4

Page 1 of 2

Item	Revision or Clarification
1.	<p>Section 2.4. Analyses and Amendment 3, Item 1.</p> <p><u>Change to:</u></p> <p>Principal Investigator (Formulation Analysis): Devon Kyle, B.S.</p> <p>Telephone: 814-272-1039 ext. 4339</p> <p>Telefax: 814-231-1580</p> <p>E-mail: devon.kyle@mpiresearch.com</p>
Item	Justification
1.	Principal Investigator updated due to change in personnel.

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 4

Page 2 of 2

Approved by:

11-Mar-2011

Date of Sponsor
Approval

Lisa Craig

Lisa Craig, B.S.
Study Director

14-Mar-2011

Date

James G. Laveglia

James G. Laveglia, Ph.D.
Executive Vice President Drug Safety Evaluation

3/16/11

Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 5

Page 1 of 2

Item	Revision or Clarification
1.	<p>Section 2.3. Test Article Analysis – Analytical Sample Collection Table</p> <p><u>Add:</u></p> <p>Concentration samples will also be collected per protocol from the Weeks 47 and 48 preparations and analyzed.</p> <p>Effective Date: June 9, 2011 and June 21, 2011</p>
2.	<p>Section 2.4. Analyses</p> <p><u>Add:</u></p> <p>Acceptance criteria for solutions will be $\pm 10\%$ for recovery and $\leq 10\%$ RSD for precision.</p> <p>Effective Date: June 29, 2011</p>
3.	<p>6.6.5. Peripheral Blood Smears</p> <p><u>Add:</u></p> <p>Animals having blood samples collected for use in blood smear preparations only will not be fasted overnight prior to sample collection.</p> <p>Effective Date: July 27, 2011</p>

Item	Justification
1.	Additional intervals added due to previous preparations failing to meet recovery.
2.	Acceptance criteria added per Sponsor request.
3.	Clarification to protocol.

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 5

Page 2 of 2

Approved by:

30 Apr - 2012

Date of Sponsor
Approval

Lisa Craig

Lisa Craig, B.S.
Study Director

30-Apr-2012

Date

Scott Boley

Scott Boley, Ph.D., D.A.B.T.
Senior Director, General Toxicology and
Infusion

30 Apr 2012

Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 6

Page 1 of 3

Item	Revision or Clarification											
1. Section 4. Study Design												
G R O U P			Initial		Clinical Pathology ^a		Number of Animals				Microscopic Pathology ^c	
							12-Month Interim Necropsy ^{a, b}		Terminal Necropsy ^d			
	Dose Level (mg/kg/day)		M	F	M	F	M	F	M	F	M	F
	1	0	80	80	10	10	10	10	70	70	80	80
	2	0.1	80	-	10	-	10	-	70	-	AR	-
3	1	80	80	10	10	10	10	70	70	AR	AR	
4	50	80	80	10	10	10	10	70	70	80	AR	
5	500	-	80	-	10	-	10	-	70	-	80	
89*	-	25	25	-	-	-	-	-	-	-	-	

a: Hematology, and clinical chemistry will be performed on 10 animals/sex/group at 3 months.

Hematology, coagulation, clinical chemistry, and urinalysis evaluations will be conducted on 10 animals/sex/group at 6 and 12 months. Differential blood smear will be prepared on all animals designated for necropsy at 12 months, all survivors at 12, 18, and 24 months (termination), and all animals euthanized in extremis.

b: An interim necropsy will be conducted at 12 months on 10 animals/sex/group.

c: Animals from both the 12 month interim and terminal necropsies, and other animals as required..

d: The animals will be terminated early once survival for any group reaches 15 remaining animals.

AR = As Required: 1) Target tissues identified by high dose group evaluations, 2) Tissues in all animals found dead or euthanized in a moribund condition, and 3) gross lesions.

*Sentinel animals

Effective Date: July 2, 2012

2. Peripheral Blood Smears

Section 6.6.5.2. Collection Intervals

12 and 18 months and **prior to termination** (~~24 months~~)

Peripheral blood smears will be prepared and held for possible future analysis from all surviving animals at 12, 18, and ~~24 months~~ **prior to study termination**.

Effective Date: July 2, 2012

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 6

Page 2 of 3

Item	Revision or Clarification
3.	<p>Section 8. Postmortem Evaluations</p> <p>At the appropriate intervals (after 12 and 24 months or at early termination), all appropriate animals will be euthanized and examined.</p>

Effective Date: July 2, 2012

Item	Justification
1-3.	<p>Per discussions with the Sponsor, all surviving animals of a given sex will be termed once survival of that sex in any group reaches 15 remaining. This is to ensure at least 25% survival (13/50) so that the carcinogenicity endpoints can be accurately evaluated.</p>

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 6

Page 3 of 3

Approved by:

Susan A. McKenzie 7/11/12
Date of Sponsor
Approval

Lisa Craig
Lisa Craig, B.S.
Study Director

11-Jul-2012
Date

Scott E Boley
Scott Boley, Ph.D., D.A.B.T.
Senior Director, General Toxicology and
Infusion

11 July 2012
Date

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 7

Page 1 of 2

Item	Revision or Clarification
1.	<p>Section 8. Postmortem Study Evaluations</p> <p>Add:</p> <p>The liver (both sexes) and kidneys (females only) are potential target organs and will be examined on all animals on study at the interim necropsy.</p> <p>The liver, pancreas, testes, and tongue are potential target organs and will be examined on all male animals in Groups 2 and 3 at the terminal necropsy.</p> <p>The tongue, pancreas, stomach (non-glandular limiting ridge), adrenal glands, lung, and uterus with cervix are potential target organs and will be examined on all female animals in Groups 3 and 4 at the terminal necropsy.</p> <p>Add:</p> <p>A pathologist other than the study pathologist will perform a formal peer review of the histopathologic findings. This review will consist of an examination of all tissues determined to be target organs by the study pathologist, all neoplasms diagnosed in the study and all tissues from 10% of the animals selected randomly from control and high dose groups. Other selected tissues may be examined at the discretion of the reviewing pathologist. A signed statement by the reviewing pathologist will appear in the final report.</p> <p>The slides for the 10% control and high dose animals and the livers and kidneys for all females will be shipped to the following for completion of the pathology peer review:</p> <p>Carolyn Lloyd, S320/525 1090 Elkton Road Newark, DE 19714-0050 Ph. 302-366-5401 Fax 302-451-4530 carolyn.w.lloyd@usa.dupont.com</p> <p>Effective Date: October 17, 2012</p>

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage
Study in Rats

Protocol Amendment No. 7

Page 2 of 2

Item	Justification
1.	Potential target organs added and slide shipment information added.

Approved by:

15-Nov-2012
Date of Sponsor
Approval

Lisa Craig
Lisa Craig, B.S.
Study Director

20 Nov-2012
Date

Scott E Boley
Scott Boley, Ph.D., D.A.B.T.
Senior Director, General Toxicology and
Infusion

20 Nov 2012
Date

MPI Research Study Number: 125-141

DuPont Work Request/Study Code Number: DuPont-18405-1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 8

Page 1 of 1

Item	Revision or Clarification
------	---------------------------

1. **Section 9.5. Tumor Analysis**

Change to:

Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at a 0.05 significance level	Common and rare tumors will be tested at a 0.05 significance level

Item	Justification
------	---------------

1. Clarification of the significance level for tumor analysis.

Approved by:

10 - Jan - 2013

Date of Sponsor
Approval

Lisa Craig

Lisa Craig, B.S.
Study Director

31 - Jan - 2013

Date

Scott Boley

Scott Boley, Ph.D., D.A.B.T.
Senior Director, General Toxicology and
Infusion

30 Jan 2013

Date

MPI Research Study Number: 125-141
DuPont Study Number: DuPont-18405/1238

Title: H-28548: Combined Chronic Toxicity/Oncogenicity Study 2-Year Oral Gavage Study in Rats

Protocol Amendment No. 9

Page 1 of 1

Item	Revision or Clarification
------	---------------------------

1. Section 11. Data and Specimen Retention

Update to:

All raw data, documentation, records, protocol, specimens, samples and the final report generated as a result of this study will be retained at MPI Research or an MPI Research contracted archive facility for a period of 1 year following the issuance of the draft report. The Sponsor will be contacted annually by MPI Research Archive staff regarding the retained material and will be responsible for the incurred costs for the return, disposal, or continued storage of any study generated material retained after that time. **The tissue slides sent for pathology peer review to the Sponsor will be archived at that site.**

Item	Justification
------	---------------

1. Additional specimen retention instructions added.

Approved by:

25-Mar-2013
Date of Sponsor
Approval

Lisa Craig
Lisa Craig, B.S.
Study Director

25-Mar-2013
Date

Scott E Boley
Scott Boley, Ph.D., D.A.B.T.
Senior Director, General Toxicology and
Infusion

25Mar 2013
Date

Appendix N
Deviations

This study was conducted in accordance with the protocol except for the following deviations. Unplanned protocol deviations are listed below. The following event occurred as the result of an unintended deviation from the protocol.

On Days -14 and -13, two banks of animal cages were found to be disconnected from the automatic water line during the morning cageside observation on Day -13. The evening cageside observation on Day -14 was performed at 16:30 and the Day -13 morning cageside observation was performed at 07:10.

On Day -6, the humidity in the animal room was documented at 73.17%.

On Days -7, 78, and 456, the lot numbers for the basal laboratory diet were incorrectly entered; therefore, there is no documentation of the exact lot numbers in the study data.

On Day 140, the temperature in the animal room was documented at 62.98°F.

Between Days 174 to 357, blood smears were not collected for the following animals euthanized *in extremis*: three males at 0.1 mg/kg/day (1111, 1145, and 1155), three males at 1 mg/kg/day (animal numbers 1190, 1230, and 1237), one male at 50 mg/kg/day (animal number 1284), four females at 0 mg/kg/day (animal numbers 1341, 1371, 1373, and 1399), two females at 1 mg/kg/day (animal numbers 1421 and 1458), three females at 50 mg/kg/day (animal numbers 1513, 1518, and 1556), and two females at 500 mg/kg/day (animal numbers 1580 and 1610).

On Day 183, the animals designated for the 6 month urinalysis collections were not fasted for the entirety of the sample collection.

On Day 253, the first dose of the day began at 12:03, instead of occurring in the AM.

On Day 294 (Week 42), the Week 43 formulations were completed without taking the appropriate formulation samples. The samples were taken during Week 44 for this interval instead.

On Day 328, the first dose of the day began at 12:00, instead of occurring in the AM.

On Days 330 and 337, the lot numbers for the basal laboratory diet were incorrectly entered; therefore, there is no documentation of the exact lot numbers in the study data.

On Day 337, food was not available *ad libitum* for one male at 1 mg/kg/day (animal number 1217) and two males at 50 mg/kg/day (animal numbers 1283 and 1309) at the morning cageside observation.

On Day 341, food was not available *ad libitum* for one male at 0 mg/kg/day (animal number 1071) at the morning cageside observation.

On Day 344 (Week 50), the food consumption was incorrectly calculated for Group 1 males (last 10 cages), Group 1 females, all males in Groups 2, 3, and 4, and the last 20 cages in Group 5. The values for this week were excluded from the data.

On Day 357, the humidity in the animal room was documented at 74.67% and 72.77%.

On Day 369, the blood sample collected from one female at 50 mg/kg/day (animal number 1481) was collected via cardiac puncture after carbon dioxide inhalation.

On Day 374, the first dose of the day began at 13:22, instead of occurring in the AM.

On Day 378, the first dose of the day began at 12:03, instead of occurring in the AM.

From Days 429 to 449, food consumption was not calculated for one female at 50 mg/kg/day (animal number 1502).

On Day 462, the harderian gland was fixed in modified Davidson's fixative for one female at 0 mg/kg/day (animal number 1375), one male at 1 mg/kg/day (animal number 1189), one male at 50 mg/kg/day (animal number 1259), and one female at 500 mg/kg/day (animal number 1635) euthanized *in extremis*.

On Day 573, the first dose of the day began at 12:06, instead of occurring in the AM.

On Day 602, the blood smear for one male at 0 mg/kg/day (animal number 1055) euthanized *in extremis* was collected via the vena cava after carbon dioxide inhalation.

At terminal necropsy (Day 723, Week 104), the Mass A was not located at the time of tissue trimming for one male at 50 mg/kg/day (animal number 1289).

In the opinion of the Study Director, these deviations did not affect the quality or integrity of the study.